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Margaret M. Brumm
Printed Name

Margaret M. Brumm
Signature

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,808,614

Patentee : Larry W. Hertel Attn: Box Patent Ext.

Assignee : Eli Lilly and Company

Issue Date : February 28, 1989

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

Assistant Commissioner for Patents

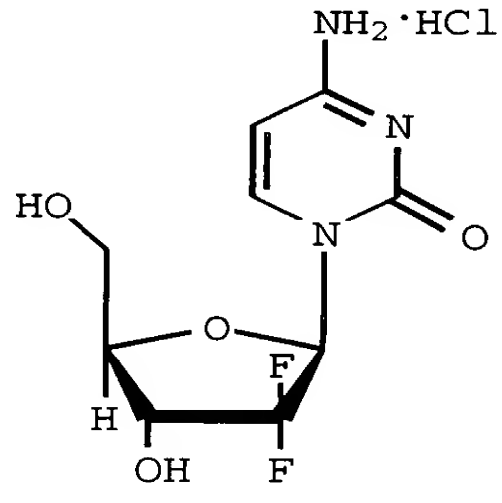
Washington, D.C. 20231

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. 156, Eli Lilly and Company, owner of the above-identified patent by an Assignment recorded on March 22, 1985, in Reel 4376, Frame 0596, hereby requests an extension of the patent term of U.S. Patent No. 4,808,614. The following information is submitted in accordance with 35 U.S.C. 156(d) and 37 C.F.R. 1.710 et seq. and follows the numerical format set forth in 37 C.F.R. 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is gemcitabine hydrochloride which has the chemical name 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer) and has the following structure:



Gemcitabine hydrochloride is the active ingredient in the product GEMZAR® as may be seen from attached Exhibit I, which is the Product Information Sheet for this product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. 301 et seq. Section 505 provides for the submission and approval of new drug applications (NDAs) for human drug products meeting the definition of "new drug" under Section 201(p) of the Act.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Gemcitabine hydrochloride was approved by the Food and Drug Administration (FDA) for commercial marketing pursuant to Section 505 of the FFDCA on May 15, 1996.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it

was approved, and the provision of law under which it was approved.

As stated in Sections 1, 2, and 3 above, the active ingredient in the product GEMZAR® is gemcitabine hydrochloride. Gemcitabine hydrochloride had not previously been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act until May 15, 1996.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted:

The product was approved on May 15, 1996 and the last day within the sixty day period permitted for submission of an application for extension of a patent is July 14, 1996. Since July 14, 1996 is a Sunday, the application may be timely filed on July 15, 1996, the next succeeding business day in accordance with 35 U.S.C. 21(b). As evident from the Certificate of Mailing by "Express Mail" pursuant to 37 C.F.R. 1.10, this application is timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. Patent No.:	4,808,614
Inventor:	Larry W. Hertel
Issued:	February 28, 1989
Expires:	February 28, 2006

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings:

A copy of the patent is attached as Exhibit II.

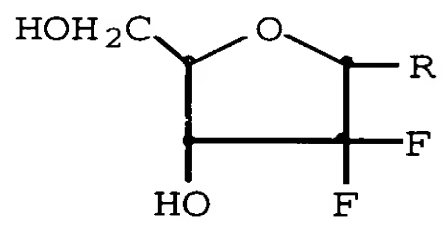
(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

A copy of the certificate of correction and receipt of maintenance fee payment made in 1992 are attached as Exhibit III. For U.S. Patent 4,808,614 there is no disclaimer or reexamination certificate issued.

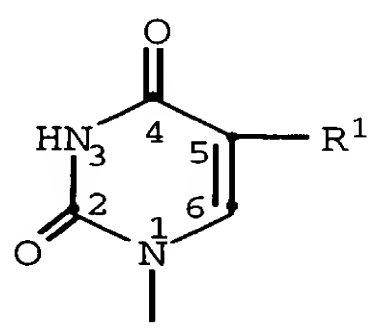
(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

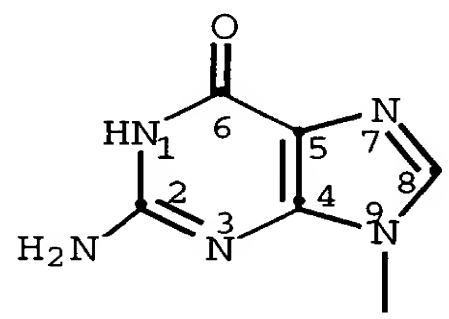
Claim 1 of U.S. Patent No. 4,808,614 reads:

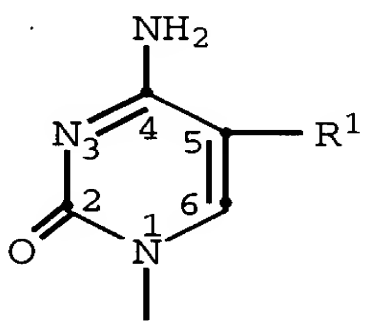
1. A nucleoside of the formula

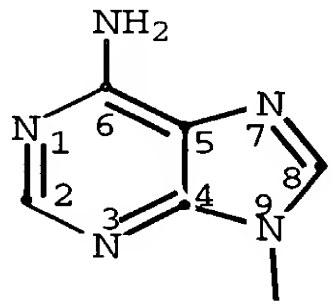


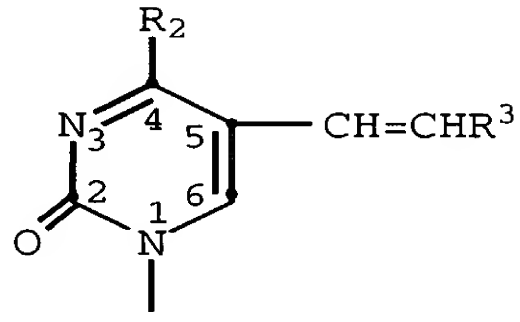
wherein R is a base selected from the group consisting of









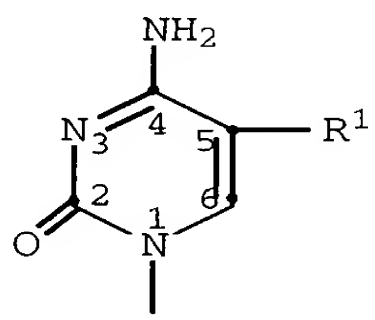


wherein

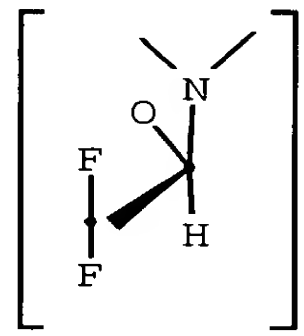
R^1 is hydrogen, methyl, bromo, fluoro, chloro or iodo;

R^2 is hydroxy;

R^3 is hydrogen, bromo, chloro or iodo.



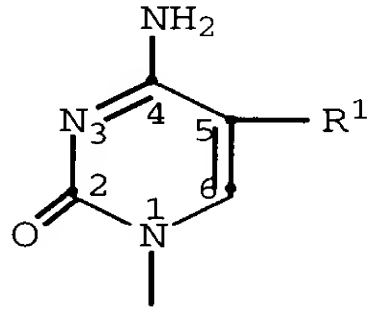
When the base R is , the carbohydrate is in the ribose configuration, the configuration of the



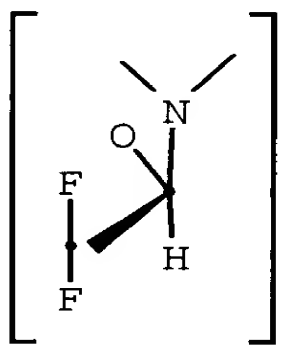
juncture between the ribose and the base is β , and R^1 is hydrogen, then Claim 1 claims gemcitabine (2'-deoxy-2',2'-difluorocytidine β-isomer).

Claim 2 claims the nucleoside of Claim 1 wherein the carbohydrate moiety is in the ribose form. Thus, when all the rest of the conditions described above for Claim 1 are met, then Claim 2 also reads on gemcitabine.

Claim 7 claims a nucleoside of Claim 1 wherein the base

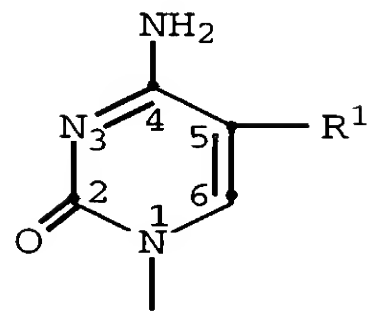


is of the formula . When the carbohydrate is in the ribose configuration, the configuration between the ribose and the



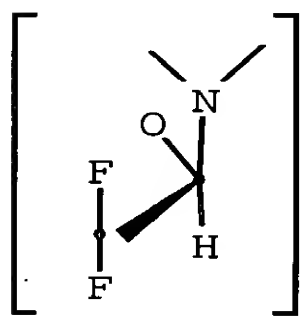
base if β, , and R^1 is hydrogen, then Claim 7 claims gemcitabine (2'-deoxy-2',2'-difluorocytidine β-isomer).

Claim 8 claims a nucleoside of Claim 2 wherein the base is of the formula



When the configuration between the ribose and the base is β, as before, and R^1 is hydrogen, then Claim 8 reads on gemcitabine.

Claim 11 is the nucleoside of Claim 7, wherein R^1 is hydrogen. When the carbohydrate is in the ribose configuration, the configuration between the ribose and the base is β,



, then Claim 11 reads on gemcitabine.

Claim 12 is the nucleoside of Claim 8, wherein R^1 is hydrogen. Therefore, Claim 12 reads on gemcitabine.

Based on the above, claims 1, 2, 7, 8, 11 and 12 of the patent all read on gemcitabine. The approved product is the hydrochloride salt of gemcitabine. In 35 U.S.C. §156(f)(1)(A) the term "product" is defined as "A drug product". In 35 U.S.C. §156(f)(2)(A) the term "drug product" is defined as "the active ingredient of (A) a new drug, antibiotic drug or human biological product (as those terms are used in the Federal Food, Drug and Cosmetic Act and the Public Health Service Act), ..., including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient". Accordingly, it is our position that under the definitions in the above cited Patent Law, Claims 1, 2, 7, 8, 11 and 12 all read on the approved product, because all of these claims read on gemcitabine and the approved product is the hydrochloride salt of gemcitabine.

(10) A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued;

(ii) For a patent claiming a new animal drug, the date a major health or environmental effects test on the drug was initiated and any available substantiation of that date or the date of an exemption under subsection (j) of section 512 of the Federal Food, Drug, and Cosmetic Act became effective for such animal drug; the date on which a new animal drug application (NADA) was initially submitted and the NADA number; and the date on which the NADA was approved;

(iii) For a patent claiming a veterinary biological product, the date the authority to prepare an experimental biological product under the Virus-Serum-Toxin Act became effective; the date an application for a license was submitted under the Virus-Serum-Toxin Act; and the date the license issued;

(iv) For a patent claiming a food or color additive, the date a major health or environmental effects test on the additive was initiated and any available substantiation of that date; the date on which a petition for product approval under the Federal Food, Drug, and Cosmetic Act was initially submitted and the petition number; and the date on which the FDA published the Federal Register notice listing the additive for use;

(v) For a patent claiming a medical device, the effective date of the investigational device exemption (IDE) and the IDE number, if applicable, or the date on which the applicant began the first clinical investigation involving the device if no IDE was submitted and any available substantiation of that date; the date on which the application for product approval or notice of completion of a product development protocol under section 515 of the Federal Food, Drug, and Cosmetic Act was initially submitted and the number of the application or protocol; and the date on which the application was approved or the protocol declared to be completed:

On January 28, 1987, Eli Lilly and Company, the assignee of U.S. Patent No. 4,808,614, submitted to the FDA a "Notice of Claimed Investigational Exemption for a New Drug" (IND) under Section 505(i) of the FFDCA to permit the interstate shipment of gemcitabine hydrochloride for the purpose of conducting clinical studies to support the approval of a subsequent New Drug Application (NDA) for gemcitabine hydrochloride. A copy of the letter transmitting the IND to the FDA is attached as Exhibit IV. By letter dated February 3, 1987, the FDA acknowledged receipt of the IND and assigned the IND number 29,653. A copy of the FDA Receipt Letter of the IND is included as Exhibit V. A clinical hold was placed on the IND by telephone call on February 27, 1987. Lifting of the clinical hold was first communicated to Lilly in a telephone call from Ms. Cathie Schumaker of the FDA on May 12, 1987. A letter from the FDA confirming the lifting of the clinical hold was sent June 18, 1987. A copy of this letter is enclosed as Exhibit VI. This correspondence establishes the beginning of the "regulatory review period" under 35 U.S.C. 156(g)(1) as June 18, 1987, which is the effective date of an exemption under Section 505(i).

Lilly submitted an NDA (part 1 of 2) for gemcitabine hydrochloride on December 22, 1994. NDA (Part 1 of 2) contains the pre-submission of chemistry, manufacturing and control data and nonclinical pharmacology and toxicology date. This pre-submission did not include the entire NDA, so it did not start the statutory period for regulatory review. A copy of the letter submitting NDA (part 1 of 2) is enclosed as Exhibit VII. NDA submission (part 1 of 2) was received by FDA on December 23, 1994 and assigned the NDA number 20-509. A copy of the receipt letter dated January 27, 1995, for NDA submission (part 1 of 2) from FDA is included as Exhibit VIII.

Lilly submitted NDA (part 2 of 2) for gemcitabine hydrochloride on February 1, 1995. A copy of the letter submitting NDA (part 2 of 2) is enclosed as Exhibit IX. NDA submission (part 2 of 2) was received by FDA on February 2, 1995. A copy of the receipt letter dated February 16, 1995, for NDA submission (part 2 of 2) from FDA is included as Exhibit X. Thus, for the purpose of the "regulatory review period" under 35 U.S.C. 156(g)(1), February 2, 1995 is the date of initial submission of a new drug application under Section 505 for gemcitabine hydrochloride.

The NDA described above was approved on May 15, 1996. Attached as Exhibit XI is a letter dated May 15, 1996 from the FDA to Lilly approving the NDA for gemcitabine hydrochloride. Thus, for the purpose of the "regulatory review period" under 35 U.S.C. 156(g)(1), May 15, 1996 is the date of approval of the NDA for gemcitabine hydrochloride submitted on February 2, 1995.

(11) A brief description, beginning on a new page, of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

During the applicable regulatory review period, Lilly was actively involved in obtaining NDA approval for gemcitabine hydrochloride. As discussed in (10) above, the IND for gemcitabine hydrochloride was submitted on January 28, 1987, the NDA was submitted on February 2, 1995, and the NDA was approved on May 15, 1996. Lilly was in close consultation with the FDA during the clinical studies conducted under the IND. Similarly, subsequent to the submission of the NDA, Lilly had numerous contacts and meetings with the FDA with respect to the approval and, in fact, conducted additional studies at FDA's request to support the NDA approval. The description of significant activities undertaken by Lilly with respect to gemcitabine hydrochloride during the regulatory review period as set forth in Exhibit XII is illustrative of the activities involved. Because Applicant is only going to be given the benefit of acts occurring after issuance of the patent (February 28, 1989) only very basic information regarding activities during the IND before the patent was granted is presented here, but more detailed information regarding this period would be available upon request from the Commissioner or Secretary.

(12) A statement that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined:

(a) Statement of eligibility of the patent for extension under 35 U.S.C. 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) The term of U.S. Patent No. 4,808,614 expires on February 28, 2006. This application has, therefore, been submitted before the expiration of the patent term.

(2) The term of this patent has never been extended.

(3) This application is submitted by the owner of record, Eli Lilly and Company (Assignment recorded on March 22, 1985, in Reel 4376, Frame 0596). This application is submitted in accordance with 35 U.S.C. 156(d) in that it is submitted within the sixty day period beginning on the date, May 15, 1996, the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. 156(d).

(4) As evidenced by the May 15, 1996 letter from the FDA (Exhibit XI), the product was subject to a regulatory review period under Section 505 of the FFDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of gemcitabine hydrochloride after regulatory review under Section 505 is the first permitted commercial marketing of gemcitabine hydrochloride. This is confirmed by the absence of any approved new drug application for gemcitabine hydrochloride prior to May 15, 1996.

(b) Statement as to length of extension claimed:

The term of U.S. Patent No. 4,808,614 should be extended by 1537 days to May 15, 2010. This extension was determined on the following basis: as set forth in 35 U.S.C. 156(g)(1) and 37 C.F.R. 1.775(c), the regulatory review period equals the length of time between the effective date of the initial IND (June 18, 1987) and the initial submission of the NDA (February 2, 1995) a period of 2786 days, plus the length of time between the initial submission of the NDA (February 2, 1995) to NDA approval (May 15, 1996) a period of 468 days. These two periods added together equal a regulatory review period of 3254 days.

Pursuant to 35 U.S.C. 156(c) and 37 C.F.R. 1.775 (d)(1)(i), the term of the patent eligible for extension shall be extended by the time equal to the regulatory review period which occurs after the date the patent was issued. In this case, this is the period of time running from the date of patent issue, February 28, 1989, to the date of NDA approval, May 15, 1996, a period of 2633 days.

As discussed in paragraph (11) above and as illustrated in Exhibit XII, Lilly was continuously and diligently working toward securing NDA approval for gemcitabine hydrochloride. As Lilly acted with due diligence during the entire period of

regulatory review, the 2633 day period calculated above as the term of the patent eligible for extension should not be reduced for lack of diligence under 35 U.S.C. 156(c)(1) or 37 C.F.R. 1.775 (d)(1)(ii).

Pursuant to 35 U.S.C. 156(c)(2) and 37 C.F.R. 1.775(d)(1)(iii), this 2633 day period is to be reduced by one-half of the time from date of patent issue (February 28, 1989) to the date of initial submission of the NDA (February 2, 1995) a period of 2165 days. One-half of this period is 1082 days (half days will be ignored for purposes of subtraction). Thus, the 2633 day period is reduced by 1082 days leaving a revised regulatory period of 1551 days.

Pursuant to 35 U.S.C. 156(c)(3) and 37 C.F.R. 1.775(d)(2-4), if the period remaining in the term of the patent after the date of approval (May 15, 1996 to February 28, 2006, which is 3576 days), when added to the revised regulatory review period (1551 days) exceeds 14 years (5113 days), the period of extension must be reduced so that the total of both such periods does not exceed fourteen years. In this case, the total of both such periods exceeds 14 years by 14 days. Therefore, the 1551 day revised regulatory review period must be reduced by 14 days to a 1537 day period.

The period of patent term extension as calculated above is also subject to the provisions of 35 U.S.C. 156(g)(4) and 37 C.F.R. 1.775(d)(5-6). The patent to be extended issued after and clinical evaluation of the approved product began after the enactment of the statute, September 24, 1984. Since commercial marketing of the drug was approved after enactment of the statute, the five year maximum on extension as provided in 35 U.S.C.

156(g)(6)(A) and 37 C.F.R. 1.775(d)(5) is applicable. Since this maximum is greater than the period calculated above, the term of the patent is eligible for a 1537 day extension until May 15, 2010. (The year 2008 is a leap year accounting for one additional day in determining the extendible days.)

(13) A statement that applicant acknowledges a duty to disclose to the Assistant Commissioner for Patents and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (See §1.765):

Applicant acknowledges a duty to disclose to the Assistant Commissioner for Patents and the Secretary of Health and Human Services any information which is material to any determination of entitlement to the extension sought. Applicant is unaware of any such information other than that already presented in this application and attached exhibits.

(14) The prescribed fee for receiving and acting upon the application for extension (See §1.20(j)):

As indicated by the letter of transmittal submitted with this application, the Assistant Commissioner for Patents has been authorized to charge the filing fee of $1,060.00 to deposit account No. 05-0840 in the name of Eli Lilly and Company and any additional fees which may be required.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Address all correspondence to Margaret M. Brumm, Eli Lilly and Company, Patent Division/MMB, Lilly Corporate Center, Indianapolis, Indiana 46285. Direct telephone calls to Margaret M. Brumm, 317-276-0755.

(16) A duplicate of the application papers, certified as such:

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156, including its attachments and supporting papers, is being submitted with a duplicate copy thereof.

(17) An oath or declaration as set forth in 37 C.F.R. 1.740(b):

As the undersigned agent of Eli Lilly and Company, the owner of record of U.S. Patent No. 4,808,614, which, by submission of this paper and attached Exhibits, now applies for an extension of term of this patent, I, David E. Boone, declare that (1) I am a Patent Attorney authorized to practice before the Patent and Trademark Office and have general authority from Eli Lilly and Company to act on its behalf in patent matters; that (2) I have reviewed and understand the contents of this application for extension of U.S. Patent No. 4,808,614; that (3) I believe the patent is subject to extension pursuant to 37 C.F.R. 1.710; that (4) I believe the length of extension claimed is fully justified under 35 U.S.C. 156 and applicable regulations; and that (5) I believe the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. 1.720.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent extension issuing thereon.

I hereby appoint as United States attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: David E. Boone, Reg. No. 27,857, Robert A. Conrad, Reg. No. 32,089, and Margaret M. Brumm,

Reg. No. 33,655, said David E. Boone, Reg. No. 27,857 to have in addition full power of revocation, including the power to revoke the power herein granted to said Robert A. Conrad and Margaret M. Brumm.

ELI LILLY AND COMPANY

By: _____
David E. Boone
Assistant Secretary
Deputy General Counsel
General Patent Counsel
Registration No. 27,857
Phone: 317-276-3881

Eli Lilly and Company
Patent Division/MMB
Lilly Corporate Center
Indianapolis, Indiana 46285

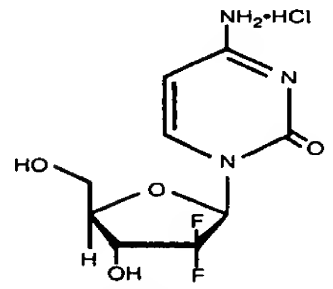
July 10, 1996

GEMZAR®
(GEMCITABINE HCl)
FOR INJECTION

DESCRIPTION

Gemzar® (gemcitabine HCl) is a nucleoside analogue that exhibits antitumor activity. Gemcitabine HCl is 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (ß-isomer).

The structural formula is as follows:



The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4 \cdot HCl$. It has a molecular weight of 299.66.

Gemcitabine HCl is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

CLINICAL PHARMACOLOGY

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

Human Pharmacokinetics—Gemcitabine disposition was studied in five patients who received a single 1000 mg/m²/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2′-deoxy-2′,2′-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma. Gemcitabine plasma protein binding is negligible.

The pharmacokinetics of gemcitabine were examined in 353 patients, about 2/3 men, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusions (70 to 285 minutes). The total Gemzar dose varied from 500 to 3600 mg/m².

Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Clearance was affected by age and gender. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 1 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 1
Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance Men (L/hr/m²)	Clearance Women (L/hr/m²)	Half-Life[a] Men (min)	Half-Life[a] Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

[a]Half-life for patients receiving a short infusion (<70 min)

Gemcitabine half-life for short infusions ranged from 32 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m² following infusions lasting <70 minutes, indicating that gemcitabine, after short infusions, is not extensively distributed into tissues. For long infusions, the volume of distribution rose to 370 L/m², reflecting slow equilibration of gemcitabine within the tissue compartment.

The maximum plasma concentrations of dFdU (inactive metabolite) were achieved up to 30 minutes after discontinuation of the infusions and the metabolite is excreted in urine without undergoing further biotransformation. The metabolite did not accumulate with weekly dosing, but its elimination is dependent on renal excretion, and could accumulate with decreased renal function.

The effects of significant renal or hepatic insufficiency on the disposition of gemcitabine have not been assessed.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

CLINICAL STUDIES

Data from two clinical trials evaluated the use of Gemzar in patients with locally advanced or metastatic pancreatic cancer. The first trial compared Gemzar to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial studied the use of Gemzar in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of Gemzar was administered intravenously at a dose of 1000 mg/m² over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with Gemzar. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

The primary efficacy parameter in these studies was "clinical benefit response", which is a measure of clinical improvement based on analgesic consumption, pain intensity, performance status and weight change. Definitions for improvement in these variables were formulated prospectively during the design of the two trials. A patient was considered a clinical benefit responder if either:

i) the patient showed a ≥50% reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a twenty point or greater improvement in performance status (Karnofsky Performance Scale) for a period of at least four consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as four consecutive weeks with either any increase in pain intensity or analgesic consumption or a 20 point decrease in performance status occurring during the first 12 weeks of therapy.

OR:

ii) the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain (≥ 7% increase maintained for ≥ 4 weeks) not due to fluid accumulation.

The first study was a multicenter (17 sites in US and Canada), prospective, single-blinded, two-arm, randomized, comparison of Gemzar and 5-FU in patients with locally advanced or metastatic pancreatic cancer who had received no prior treatment with chemotherapy. 5-FU was administered intravenously at a weekly dose of 600 mg/m² for 30 minutes. The results from this randomized trial are shown in Table 2. Patients treated with Gemzar had statistically significant increases in clinical benefit response, survival, and time to progressive disease compared to 5-FU. The Kaplan-Meier curve for survival is shown in Figure 1. No confirmed objective tumor responses were observed with either treatment.

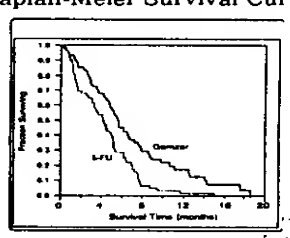
Table 2
Gemzar Versus 5-FU in Pancreatic Cancer

	Gemzar	5-FU	
Number of patients	63	63	
Male	34	34	
Female	29	29	
Median age	62 years	61 years	
Range	37 to 79	36 to 77	
Stage IV disease	71.4%	76.2%	
Baseline KPS[a] ≤70	69.8%	68.3%	
Clinical benefit response	22.2% (N[c] = 14)	4.8% (N = 3)	p = 0.004
Survival			p = 0.0009
Median	5.7 months	4.2 months	
6-month probability[b]	(N = 30) 46%	(N = 19) 29%	
9-month probability[b]	(N = 14) 24%	(N = 4) 5%	
1-year probability[b]	(N = 9) 18%	(N = 2) 2%	
Range	0.2 to 18.6 months	0.4 to 15.1+ months	
95% C.I. of the median	4.7 to 6.9 months	3.1 to 5.1 months	
Time to Progressive Disease			p = 0.0013
Median	2.1 months	0.9 months	
Range	0.1+ to 9.4 months	0.1 to 12.0+ months	
95% C.I. of the median	1.9 to 3.4 months	0.9 to 1.1 months	

[a]Karnofsky Performance Status
[b]Kaplan-Meier estimates
[c]N = number of patients
+ No progression at last visit; remains alive.

The p-value for clinical benefit response was calculated using the 2-sided test for difference in binomial proportions. All other p-values were calculated using the Log Rank test for difference in overall time to an event.

Figure 1
Kaplan-Meier Survival Curve



Clinical benefit response was achieved by 14 patients treated with Gemzar and patient on the Gemzar arm showed improvement in all three primary parameters (tion, and performance status). Eleven patients on the Gemzar arm and two patients ment in analgesic consumption and/or pain intensity with stable performance status showed improvement in analgesic consumption or pain intensity with improvement i on the 5-FU arm was stable with regard to pain intensity and analgesic consumption status. No patient on either arm achieved a clinical benefit response based on weig

The second trial was a multicenter (17 US and Canadian centers), open-label st advanced pancreatic cancer previously treated with 5-FU or a 5-FU-containing reg benefit response rate of 27% and median survival of 3.9 months.

When Gemzar was administered more frequently than once weekly or with i increased toxicity was observed. Results of a Phase 1 study of Gemzar to assess th on a daily x 5 schedule showed that patients developed significant hypotension a were intolerable at doses above 10 mg/m². The incidence and severity of these event studies using a twice-weekly schedule reached MTDs of only 65 mg/m² (30-minute i bolus). The dose-limiting toxicities were thrombocytopenia and flu-like symptoms, study to assess the maximum tolerated infusion time, clinically significant toxicity, seen with weekly doses of 300 mg/m² at or above a 270-minute infusion time. The ha by the length of the infusion (*see* Clinical Pharmacology) and the toxicity appears t istered more frequently than once weekly or with infusions longer than 60 minute

In a single trial where Gemzar at a dose of 1000 mg/m² was administered for u currently with therapeutic thoracic radiation to patients with NSCLC, significant potentially life-threatening, esophagitis and pneumonitis was observed, particula umes of radiotherapy. The optimum regimen for safe administration of Gemzar w has not yet been determined (*see* Precautions).

INDICATIONS AND USAGE

Therapeutic Indication—Gemzar is indicated as first-line treatment for patie sectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the patients previously treated with 5-FU.

CONTRAINDICATION

Gemzar is contraindicated in those patients with a known hypersensitivity to t Allergic).

WARNINGS

Caution—Prolongation of the infusion time beyond 60 minutes and more freque shown to increase toxicity (*see* Clinical Studies).

Gemzar can suppress bone marrow function as manifested by leukopenia, th Adverse Reactions), and myelosuppression is usually the dose-limiting toxicity. myelosuppression during therapy. *See* Dosage and Administration for recommend

Hemolytic-Uremic Syndrome (HUS) has been reported rarely with the use of Renal)

Pregnancy—Pregnancy Category D. Gemzar can cause fetal harm when adminis citabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossific mice (about 1/200 the recommended human dose on a mg/m² basis). Gemcitabine i tions (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day i mended human dose on a mg/m² basis). Embryotoxicity was characterized by dec litter sizes, and developmental delays. There are no studies of Gemzar in pregnant pregnancy, or if the patient becomes pregnant while taking Gemzar, the patient s hazard to the fetus.

PRECAUTIONS

General—Patients receiving therapy with Gemzar should be monitored closely use of cancer chemotherapeutic agents. Most adverse events are reversible and do tion, although doses may need to be withheld or reduced. There was a greater te women, not to proceed to the next cycle.

Laboratory Tests—Patients receiving Gemzar should be monitored prior to each (CBC), including differential and platelet count. Suspension or modification of th marrow suppression is detected (*see* Dosage and Administration).

Laboratory evaluation of renal and hepatic function should be performed prior t ically thereafter.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term animal stu potential of Gemzar have not been conducted. Gemcitabine induced forward mutati (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gem using the Ames, *in vivo* sister chromatid exchange, and *in vitro* chromosomal abe unscheduled DNA synthesis *in vitro*. Gemcitabine I.P. doses of 0.5 mg/kg/day (about basis) in male mice had an effect on fertility with moderate to severe hyposperma decreased implantations. In female mice, fertility was not affected but, mate 1.5 mg/kg/day I.V. (about 1/200 the human dose on a mg/m² basis) and fetotoxicity at 0.25 mg/kg/day I.V. (about 1/1300 the human dose on a mg/m² basis).

Pregnancy—Category D. *See* Warnings.

Nursing Mothers—It is not known whether Gemzar or its metabolites are excret drugs are excreted in human milk and because of the potential for serious adverse infants, the mother should be warned and a decision should be made whether to dis the drug, taking into account the importance of the drug to the mother and the po

~~Elderly Patients—Gemzar clearance is affected by age (see Clinical Pharmacology~~ that unusual dose adjustments, (ie, other than those already recommended in th tion) are necessary in patients over 65, and, in general adverse reaction rates w below 65. Grade 3/4 thrombocytopenia was more common in the elderly.

Gender—Gemzar clearance is affected by gender (*see* Clinical Pharmacology). T unusual dose adjustments (ie, other than those already recommended in the Do are necessary in women. In general, adverse reaction rates were similar in men older women were more likely not to proceed to a subsequent cycle and to expe thrombocytopenia.

Pediatric Patients—Gemzar has not been studied in pediatric patients. Safe patients have not been established.

Patients with Renal or Hepatic Impairment—Gemzar should be used with ca renal impairment or hepatic insufficiency. Gemzar has not been studied in p hepatic impairment.

Drug Interactions—No confirmed interactions have been reported with the use action studies have been conducted.

Combination Therapy—Safe and effective regimens for the administration of radiation have not yet been determined (*See* Clinical Studies).

ADVERSE REACTIONS

Myelosuppression is the principal dose-limiting factor with Gemzar therapy. Do toxicity are frequently needed and are described in the Dosage and Administratio

Data in Table 3 are based on 22 clinical studies (N = 979) of Gemzar administere doses in the range of 800 to 1250 mg/m² administered weekly as a 30-minute infusi of malignancies. Data are also shown for the subset of patients with pancreatic c The frequency of all grades and severe (WHO Grade 3 or 4) adverse events wer safety database and the subset of patients with pancreatic cancer. Adverse reactio resulted in discontinuation of Gemzar therapy in about 10% of patients. In the com rate for adverse reactions was 14.3% for the gemcitabine arm and 4.8% for the 5-F

All WHO-graded laboratory events are listed in Table 3, regardless of causali listed in Table 3 or discussed below were those reported, regardless of causality, for the categories of Extravasation, Allergic, and Cardiovascular and certain specific ev and Infection categories. Table 4 presents the data from the comparative trial o adverse events as Table 3, regardless of incidence.

Table 3
Selected WHO-Graded Adverse Events In Patients Receivi WHO Grades (% incidence)

	All Patients[a]			Pancreatic Cancer	
	All Grades	Grade 3	Grade 4	All Grades	Grade 3
Laboratory[d]					
Hematologic					
Anemia	68	7	1	73	8
Leukopenia	62	9	<1	64	8
Neutropenia	63	19	6	61	17
Thrombocytopenia	24	4	1	36	7
Hepatic					
ALT	68	8	2	72	10
AST	67	6	2	78	12
Alkaline Phosphatase	55	7	2	77	16
Bilirubin	13	2	<1	26	6
Renal					
Proteinuria	45	<1	0	32	<1
Hematuria	35	<1	0	23	0
BUN	16	0	0	15	0
Creatinine	8	<1	0	6	0
Nonlaboratory[e]					
Nausea and Vomiting	69	13	1	71	10
Pain	48	9	<1	42	6
Fever	41	2	0	38	2
Rash	30	<1	0	28	<1
Dyspnea	23	3	<1	10	0
Constipation	23	1	<1	31	3
Diarrhea	19	1	0	30	3
Hemorrhage	17	<1	<1	4	2
Infection	16	1	<1	10	2
Alopecia	15	<1	0	16	0
Stomatitis	11	<1	0	10	<1
Somnolence	11	<1	<1	11	2
Paresthesias	10	<1	0	10	<1

Grade based on criteria from the World Health Organization (WHO)
[a]N = 699-974; all patients with data
[b]N = 161-241; all pancreatic cancer patients with data
[c]N = 979
[d]Regardless of causality
[e]Table includes nonlaboratory data with incidence for all patients ≥10%. For approximately 60% o graded only if assessed to be possibly drug-related.

PA 1630 AMP

GEMZAR®
(GEMCITABINE HCl)

#4

#3

Table 4

ected WHO-Graded Adverse Events from Comparative Trial of Gemzar and 5-FU
WHO Grades (% Incidence)

	Gemzar[a]			5-FU[b]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	65	7	3	45	0	0
	71	10	0	15	2	0
a	62	19	7	18	2	3
penia	47	10	0	15	2	0
	72	8	2	38	0	0
	72	10	2	52	2	0
phatase	71	16	0	64	10	3
	16	2	2	25	6	3
	10	0	0	2	0	0
	13	0	0	0	0	0
	6	0	0	10	0	0
	2	0	0	0	0	0
Nonlaboratory[d]						
Nausea and Vomiting	64	10	3	58	5	0
Pain	10	2	0	7	0	0
Fever	30	0	0	16	0	0
Rash	24	0	0	13	0	0
Dyspnea	6	0	0	3	0	0
Constipation	10	3	0	11	2	0
Diarrhea	24	2	0	31	5	0
Hemorrhage	0	0	0	2	0	0
Infection	8	0	0	3	2	0
Alopecia	18	0	0	16	0	0
Stomatitis	14	0	0	15	0	0
Somnolence	5	2	0	7	2	0
Paresthesias	2	0	0	2	0	0

Grade based on criteria from the World Health Organization (WHO)
[a]N = 58-63; all Gemzar patients with data
[b]N = 61-63; all 5-FU patients with data
[c]Regardless of causality
[d]Nonlaboratory events were graded only if assessed to be possibly drug-related.

Hematologic—Myelosuppression is the dose-limiting toxicity with Gemzar, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, were reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during Gemzar therapy and dosage modified or suspended according to the degree of hematologic toxicity (*see* Dosage and Administration).

Gastrointestinal—Nausea and vomiting were commonly reported (69%) but were usually mild to moderate. Severe nausea and vomiting (WHO grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

Hepatic—Gemzar was associated with transient elevations of serum transaminases in approximately two-thirds of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose.

Renal—Mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the hemolytic uremic syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving Gemzar in clinical trials. Four patients developed HUS on Gemzar therapy, two immediately posttherapy. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

Fever—The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash—Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

Pulmonary—Dyspnea was reported in 23% of patients, severe dyspnea in 3%. Dyspnea may be due to underlying disease such as lung cancer (40% of study population) or pulmonary manifestations of other malignancies. Dyspnea was occasionally accompanied by bronchospasm (<2% of patients.) Rare reports of parenchymal lung toxicity consistent with drug induced pneumonitis have been associated with the use of Gemzar.

Edema—Edema (13%), peripheral edema (20%) and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

Flu-like Symptoms—"Flu syndrome" was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection—Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

Alopecia—Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity—There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Extravasation—Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemzar is not a vesicant.

Allergic—Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemzar should not be administered to patients with a known hypersensitivity to this drug (*see* Contraindication).

Cardiovascular—Two percent of patients discontinued therapy with Gemzar due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior history of cardiovascular disease.

OVERDOSAGE

There is no known antidote for overdoses of Gemzar. Myelosuppression, paresthesias and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m² was administered by IV infusion over 30 minutes every 2 weeks to several patients in a Phase 1 study. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

DOSAGE AND ADMINISTRATION

Gemzar is for intravenous use only.

Adults—Gemzar should be administered by intravenous infusion at a dose of 1000 mg/m² over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks. Dosage adjustment is based upon the degree of hematologic toxicity experienced by the patient (*see* Warnings). Clearance in women and the elderly is reduced and women were somewhat less able to progress to subsequent cycles (see Human Pharmacokinetics and Precautions).

Patients receiving Gemzar should be monitored prior to each dose with a complete ferential and platelet count. If marrow suppression is detected, therapy should be to the guidelines in Table 5.

Table 5
Dosage Reduction Guidelines

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)
≥1,000	and	≥100,000
500 - 999	or	50,000 - 99,000
<500	or	<50,000

Laboratory evaluation of renal and hepatic function, including transaminases and formed prior to initiation of therapy and periodically thereafter. Gemzar should patients with evidence of significant renal or hepatic impairment.

Patients who complete an entire 7 week initial cycle of Gemzar therapy or a sub 1000 mg/m² may have the dose for subsequent cycles increased by 25% (to 1250 m granulocyte count (AGC) and platelet nadirs exceed 1500 x 10^6/L and 100,000 x 10^6 tologic toxicity has not been greater than WHO Grade 1. If patients tolerate the s dose of 1250 mg/m², the dose for the next cycle can be increased to 1500 mg/m², p platelet nadirs exceed 1500 x 10^6/L and 100,000 x 10^6/L, respectively, and again, i been greater than WHO Grade 1.

Gemzar may be administered on an outpatient basis.

Instructions for Use/Handling—The recommended diluent for reconstitution of Injection without preservatives. Due to solubility considerations, the maximum conc stitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200 mg vial o Injection to the 1 g vial. Shake to dissolve. These dilutions each yield a gemcitabine appropriate amount of drug may be administered as prepared or further diluted wit to concentrations as low as 0.1 mg/ml.

Reconstituted Gemzar is a clear, colorless to light straw-colored solution. After Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. visually for particulate matter and discoloration, prior to administration, whenev particulate matter or discoloration is found, do not administer.

When prepared as directed, Gemzar solutions are stable for 24 hours at controlle (68° to 77°F) [*See* USP]. Discard unused portion. Solutions of reconstituted Gemz crystallization may occur.

The compatibility of Gemzar with other drugs has not been studied. No incompat infusion bottles or polyvinyl chloride bags and administration sets.

Unopened vials of Gemzar are stable until the expiration date indicated on the p room temperature 20° to 25°C (68° to 77°F) [*See* USP].

Caution should be exercised in handling and preparing Gemzar solutions. The Gemzar solution contacts the skin or mucosa, immediately wash the skin thoroughly mucosa with copious amounts of water. Although acute dermal irritation has not two of three rabbits exhibited drug-related systemic toxicities (death, hypoactivity, ing) due to dermal absorption.

Procedures for proper handling and disposal of anti-cancer drugs should be consi subject have been published.[1-7] There is no general agreement that all of the proced lines are necessary or appropriate.

HOW SUPPLIED

Vials:
200 mg white, lyophilized powder in a 10 mL size sterile single use vial (No. 7501
1 g white, lyophilized powder in a 50 mL size sterile single use vial (No. 7502) NE

Store at controlled room temperature (20° to 25°C) (68° to 77°F). The USP has defi as "A temperature maintained thermostatically that encompasses the usual and cu 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in houses."

CAUTION—Federal (USA) law prohibits dispensing without prescription.

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ELI LILLY AND COMPANY
Indianapolis, IN 46285, USA

EXHIBIT II

U.S. Patent No. 4,808,614

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

February 26, 1996

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *4,808,614*
ISSUE DATE: *February 28, 1989*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. SWAIN
Certifying Officer

United States Patent [19]

Hertel

[11] **Patent Number: 4,808,614**

[45] **Date of Patent: Feb. 28, 1989**

[54] **DIFLUORO ANTIVIRALS AND INTERMEDIATE THEREFOR**

[75] Inventor: **Larry W. Hertel**, Indianapolis, Ind.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[21] Appl. No.: **58,219**

[22] Filed: **Jun. 4, 1987**

Related U.S. Application Data

[60] Division of Ser. No. 677,146, Dec. 4, 1984, Pat. No. 4,692,434, which is a continuation-in-part of Ser. No. 473,883, Mar. 10, 1983, Pat. No. 4,526,988.

[51] **Int. Cl.**[4] **A61K 31/505; A61K 31/52**

[52] **U.S. Cl.** **514/45;** 514/46; 514/49; 514/50; 536/23; 536/24; 536/26

[58] **Field of Search** 536/23, 24, 26; 514/49, 514/45, 46, 50

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Adamson et al., *Carbohydrate Research* 18, 345–47 (1971).

Hough et al., *J. Chem. Soc. Perkin I,* 784–788 (1972).

Masamune, Sharpless et al., *J. Org. Chem.* 47, 1373–81 (1982).

Abstract, Spring 1983 ACS meeting at Seattle, D. E. Bergstrom.

Primary Examiner—John W. Rollins
Assistant Examiner—W. Catchpole
Attorney, Agent, or Firm—Joseph A. Jones; Leroy Whitaker

[57] **ABSTRACT**

A 2,2-difluoro-2-desoxycarbohydrate is used to prepare antiviral nucleosides.

14 Claims, No Drawings

DIFLUORO ANTIVIRALS AND INTERMEDIATE THEREFOR

CROSS-REFERENCE TO RELATED APPLICATION

This application is a division of application Ser. No. 677,146, filed 12/4/84, now U.S. Pat. No. 4,692,434, which is a continuation-in-part of application Ser. No. 473,883, filed 3/10/84, now U.S. Pat. No. 4,526,988.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention belongs to the field of pharmaceutical chemistry, and provides a new difluoro carbohydrate and new antiviral nucleosides prepared by coupling the new carbohydrate with appropriate bases.

2. State of the Art

It has been known for some time that antiviral drugs can be found among the general family of nucleosides. For example, 5-(2-bromovinyl)-2'-deoxyuridine is known to be a potent agent against herpes virus. DeClercq et al., *Proc. Natl. Acad. Sci. U.S.A.* 76, 2947-51 (1979). Watanabe et al. have described a number of nucleosides formed by coupling 2-fluoro-2-deoxyarabinofuranose with bases of the cytosine and thymine groups; 5-iodocytosine was their most preferred base. *J. Med. Chem.* 22, 21–24 (1979), and U.S. Pat. No. 4,211,773.

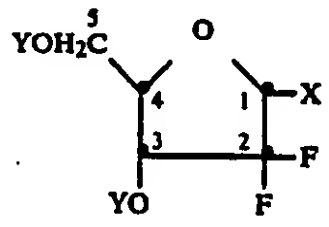
A compound which can be described as an acyclic nucleoside, 9-(2-hydroxyethoxymethyl)guanine, is a potent antiviral agent, especially useful against herpes viruses, and is the subject of a symposium in a special issue of *American Journal of Medicine*, July 1982.

Fluorinated carbohydrates have been studied before. A survey of the subject by Penglis is in *Advances in Carbohydrate Chemistry and Biochemistry* 38, 195–285 (1981). A 2,2-difluorohexose was described by Adamson et al., *Carbohydrate Research* 18, 345–47 (1971). Wright and Taylor, *Carbohydrate Research* 6, 347–54 (1968), taught the synthesis of 9-(3-deoxy-3-fluoro-α-D-arabinofuranosyl)adenine.

Recently the total synthesis of carbohydrates has become the subject of research, and a few papers have appeared. The synthesis requires stereospecific methods, and asymmetric epoxidation and asymmetric aldol reactions have been successfully used. Masamune, Sharpless et al., *J. Org. Chem.* 47, 1373–81 (1982).

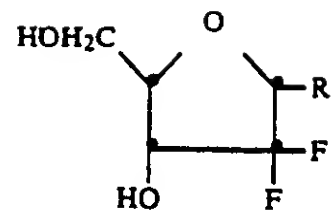
SUMMARY OF THE INVENTION

The preset invention provides the difluorodesoxy carbohydrate of the formula

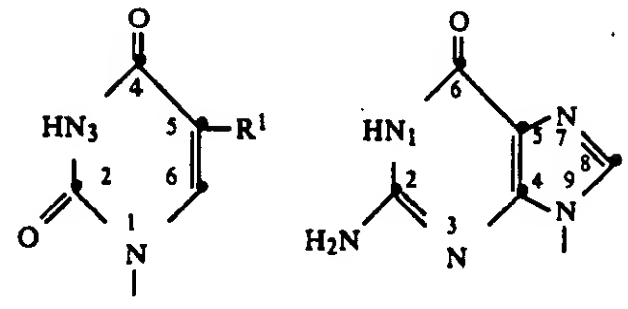


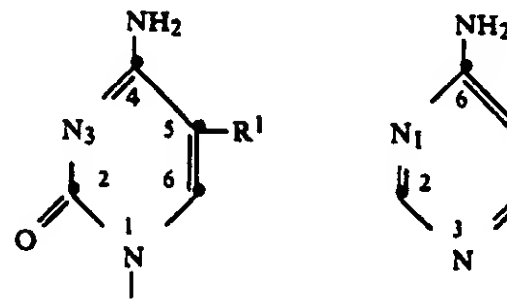
wherein X is hydroxy or a leaving group; and the Y groups independently are hydrogen or hydroxy-protecting groups.

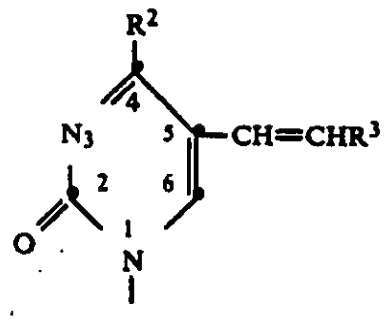
The invention also provides the nucleosides of the formula



wherein R is a base of one of the formulae







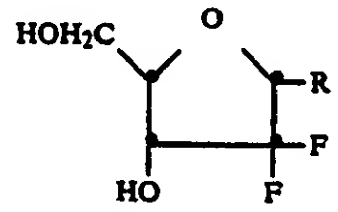
wherein

R^1 is hydrogen, methyl, bromo, fluoro, chloro or iodo;

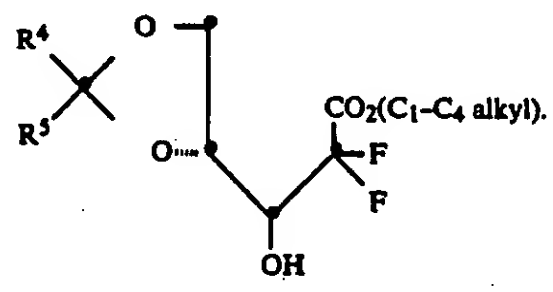
R^2 is hydroxy or amino;

R^3 is hydrogen, bromo, chloro or iodo.

The invention further comprises a process for preparing a lactone of the formula



which process comprises hydrolyzing, under very mild conditions, an alkyl 3-dioxolanyl-2,2-difluoro-3-hydroxypropionate of the formula

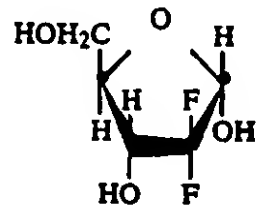


Pharmaceutical compositions comprising a nucleoside of the above formula and a pharmaceutically acceptable carrier, diluent or excipient therefor are provided as yet another aspect of the present invention, as

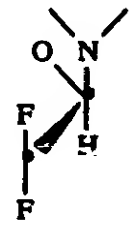
is a method of treating viral infections in mammals employing a present novel compound.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

All temperatures are described in degrees Celsius in this document. Liquids are reported in volume units. The structural drawings above do not indicate the stereochemistry of the compounds of the present invention. Compounds of all configurations are believed to be useful, and the stereochemistry of them is accordingly not a limitation. However, it is preferred that the carbohydrate have the configuration of naturally occurring ribose, as follows:



It is further preferred that the configuration of the juncture between the ribose and the base be as follows:



It is believed that pharmaceutical chemists are aware of the bases which are used in the synthesis of the antiviral nucleosides of the present invention, but the following specific nucleosides are mentioned to assure that every reader understands the type of antivirals which this invention makes available.

1-(5-methyl-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(5-bromo-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(5-chloro-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(5-iodo-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-chloro-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-bromo-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-iodo-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-[5-(2-bromovinyl)-4-hydroxy-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluororibose
1-[4-amino-5-(2-bromovinyl)-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluororibose
1-[4-amino-5-(2-iodovinyl)-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluororibose
1-[5-(2-chlorovinyl)-4-hydroxy-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluororibose
1-[4-hydroxy-5-(2-iodovinyl)-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluororibose
1-4-amino-5-(2-chlorovinyl)-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluororibose
1-(2-amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluororibose
1-(6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluororibose
1-(5-fluoro-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluoroxylose
1-(5-bromo-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluoroxylose
1-(5-chloro-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluoroxylose
1-(5-iodo-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluoroxylose
1-(4-amino-5-fluoro-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose
1-(4-amino-5-chloro-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluoroxylose
1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluoroxylose
1-(4-amino-5-fluoro-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluoroxylose
1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluoroxylose
1-[5-(2-bromovinyl)-4-hydroxy-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluoroxylose
1-[4-amino-5-(2-bromovinyl)-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluoroxylose
1-[4-amino-5-(2-iodovinyl)-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluoroxylose
1-[5-(2-chlorovinyl)-4-hydroxy-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluoroxylose
1-[4-hydroxy-5-(2-iodovinyl)-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluoroxylose
1-[4-amino-5-(2-chlorovinyl)-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluoroxylose
1-(2-amino-6-oxo-1H,9H-purin-9-yl)-2-desoxy-2,2-difluoroxylose
1-(6-amino-9H-purin-9-yl)-2-desoxy-2,2-difluoroxylose

It will be understood that the reactions in which the novel 2-desoxy-2,2-difluorocarbohydrate of this invention is coupled with the bases are frequently of a nature such that the hydroxy groups must be protected to keep them from reacting with the base, or being decomposed in some manner. The protecting groups are chosen from the groups used in synthetic organic chemistry for the purpose. Chemists are accustomed to choosing groups which can be efficiently placed on hydroxy groups, and which can be easily removed when the desired reaction is complete. Suitable groups are described in standard textbooks, such as Chapter 3 of *Protective Groups in Organic Chemistry*, McOmie, Ed., Plenum Press, New York (1973); and Chapter 2 of *Protective Groups in Organic Synthesis*, Greene, John Wiley & Sons, New York (1981).

Typical hydroxy-protecting groups include formyl, 2-chloroacetyl, benzyl, diphenylmethyl, triphenylmethyl, 4-nitrobenzyl, phenoxycarbonyl, t-butyl, methoxymethyl, tetrahydropyranyl, allyl, tetrahydrothienyl, 2-methoxyethoxymethyl, methoxyacetyl, phenoxyacetyl, isobutyryl, ethoxycarbonyl, benzyloxycarbonyl and the like. Silyl hydroxy-protecting groups are often particularly convenient, because most of them are easily cleaved by contact with water or an alcohol. Such groups include especially trimethylsilyl, as well as

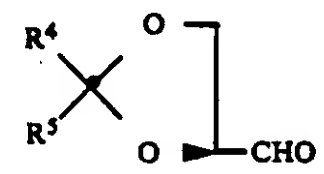
isopropyldimethylsilyl, methyldiisopropylsilyl, triisopropylsilyl and the like. The t-butyldimethylsilyl group is a special case and is preferred as the protecting group in this synthesis; it is more difficultly cleaved and requires a reagent such as a hydrohalic acid to remove it from the hydroxy groups.

Ribose or xylose has a hydroxy group at the 1-position of its ring. In order to react the carbohydrate of this invention with the base to form the antiviral compounds of the invention, it is necessary to place a leaving group at the 1-position. The leaving groups used are typical of those used commonly in organic synthesis. The preferred leaving groups are sulfonates, of which the most preferred is methanesulfonate; other typical leaving groups such as toluenesulfonate, ethanesulfonate, isopropanesulfonate, 4-methoxybenzenesulfonate, 4-nitrobenzenesulfonate, and 2-chlorobenzenesulfonate. Chloro and bromo may also be used.

The following group of representative 2-desoxy-2,2-difluorocarbohydrates of the present invention are mentioned to assure the reader's understanding.

2-desoxy-2,2-difluororibose
3,5-bis(trimethylsilyloxy)-2-desoxy-2,2-difluororibose
3,5-dibenzyloxy-2-desoxy-2,2-difluororibose
3,5-bis(chloroacetoxy)-2-desoxy-2,2-difluororibose
3,5-bis(2-chlorobenzyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose
3,5-bis(4-nitrobenzyloxy)-1-(4-toluenesulfonyloxy)-2-desoxy-2,2-difluororibose
1-chloro-3,5-bis(phenoxyacetoxy)-1,2-desoxy-2,2-difluoroxylose
1-(2,4-dibromophenylsulfonyloxy)-3,5-bis(2,2-dimethylpropionyloxy)-2-desoxy-2,2-difluoroxylose
3,5-bis(benzoyloxy)-1-(o-toluenesulfonyloxy)-2-desoxy-2,2-difluoroxylose
1-bromo-3,5-bis(methoxycarbonyloxy)-1,2-desoxy-2,2-difluoroxylose
3,5-bis(allyloxycarbonyloxy)-1-chloro-1,2-desoxy-2,2-difluoroxylose
3,5-bis(benzyloxycarbonyloxy)-2-desoxy-2,2-difluoroxylose
1-bromo-3,5-bis(4-nitrobenzyloxycarbonyloxy)-1,2-desoxy-2,2-difluoroxylose
1-bromo-3,5-bis(tetrahydrothienyloxy)-1,2-desoxy-2,2-difluororibose
1-bromo-3,5-bis(isopropyldimethylsilyloxy)-1,2-desoxy-2,2-difluororibose
1-(2-chlorophenylsulfonyloxy)-3,5-bis(methoxymethoxy)-2-desoxy-2,2-difluororibose
3,5-bis(benzyloxymethoxy)2-desoxy-2,2-difluororibose
1-(4-nitrophenylsulfonyloxy)-3,5-bis(trityloxy)-2-desoxy-2,2-difluororibose
3,5-bis(allyloxy)-1-chloro-1,2-desoxy-2,2-difluororibose
2-desoxy-2,2-difluoroxylose
3,5-bis(trimethylsilyloxy)-2-desoxy-2,2-difluoroxylose
3,5-dibenzyloxy-2-desoxy-2,2-difluoroxylose
3,5-bis(chloroacetoxy)-2-desoxy-2,2-difluoroxylose
3,5-bis(2-chlorobenzyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluoroxylose
3,5-bis(4-nitrobenzyloxy)-1-(4-toluenesulfonyloxy)-2-desoxy-2,2-difluoroxylose
1-bromo-3,5-bis(tetrahydrothienyloxy)-1,2-desoxy-2,2-difluoroxylose
1-bromo-3,5-bis(isopropyldimethylsilyloxy)-1,2-desoxy-2,2-difluoroxylose
3,5-bis(t-butyldiphenylsilyloxy)-2-desoxy-2,2-difluororibose
3,5-bis(formyloxy)-1-isopropylsulfonyloxy-2-desoxy-2,2-difluororibose
3,5-bis(trichloroacetoxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose
1-chloro-3,5-bis(phenoxyacetoxy)-1,2-desoxy-2,2-difluororibose
1-(2,4-dibromophenylsulfonyloxy)-3,5-bis(2,2-dimethylpropionyloxy)-2-desoxy-2,2-difluororibose
3,5-bis(benzoyloxy)-1-(o-toluenesulfonyloxy)-2-desoxy-2,2-difluororibose
1-bromo-3,5-bis(methoxycarbonyloxy)-1,2-desoxy-2,2-difluororibose
1-(2-chlorophenylsulfonyloxy)-3,5-bis(methoxymethoxy)-2-desoxy-2,2-difluoroxylose
3,5-bis(benzyloxymethoxy)-2-desoxy-2,2-difluoroxylose
1-(4-nitrophenylsulfonyloxy)-3,5-bis(trityloxy)-2-desoxy-2,2-difluoroxylose
3,5-bis(allyloxy)-1-chloro-1,2-desoxy-2,2-difluoroxylose
3,5-bis(t-butyldiphenylsilyloxy)-2-desoxy-2,2-difluoroxylose
3,5-bis(formyloxy)-1-isopropylsulfonyloxy-2-desoxy-2,2-difluoroxylose
3,5-bis(trichloroacetoxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluoroxylose
3,5-bis(allyloxycarbonyloxy)-1-chloro-1,2-desoxy-2,2-difluororibose
3,5-bis(benzyloxycarbonyloxy)-2-desoxy-2,2-difluororibose
1-bromo-3,5-bis(4-nitrobenzyloxycarbonyloxy)-1,2-desoxy-2,2-difluororibose

The carbohydrates are prepared by a process beginning with the reaction of a D-glyceraldehyde ketonide of the formula



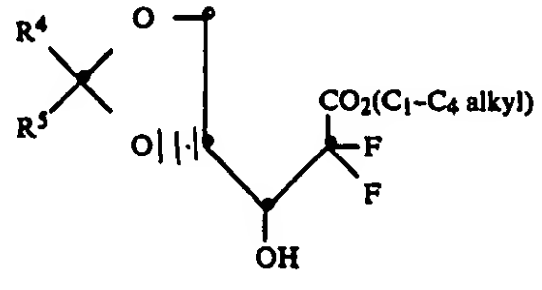
wherein R^4 and R^5 are independently C_1–C_3 alkyl, with a C_1–C_4 alkyl bromodifluoroacetate, preferably the ethyl ester.

The preferred glyceraldehyde ketonide is the acetonide wherein R^4 and R^5 are both methyl, which was first published by Fischer and Baer, *Helv. Chim. Acta.* 17, 622 (1934). Ethyl bromodifluoroacetate was first prepared by Morel and Dawans, Tet. 33, 1445 (1977). The reaction of the ketonide and the haloacetate is carried out in the presence of an activated metal such as magnesium or preferably, zinc. The activation is most easily obtained by applying ultrasonic energy to the reaction mixture. Activation by that means compensates for the presence of a small amount of water in the reaction mixture, avoiding the necessity to maintain anhydrous conditions, and also avoids the necessity to prepare and carefully store activated metals. However, the metal may be activated by the customary methods used in the art if desired. Approximately an equimolar amount of metal is the most advantageous amount.

The reaction has been performed in ethers such as tetrahydrofuran and diethyl ether, at moderate temperatures. However, other organic solvents which are inert to the reaction conditions may be employed, including halogenated alkanes such as chloroform, dichloromethane, trichloroethane and the like, and aromatics including such solvents as benzene, toluene and the xylenes. Temperatures in the range of from about ambient tem-

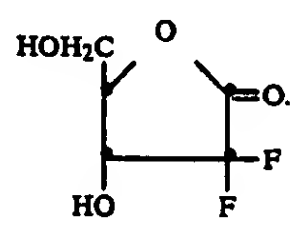
perature to about 100° are convenient; temperatures from about the ambient temperature to about 80° are preferred. Economically acceptable yields have been obtained in reaction times in the range of from a few minutes to a few hours. It should be noted that the reaction is exothermic, and the mixture may therefore need to be cooled, depending on the scale of the reaction and the rate at which the reactants are added.

The product of the first reaction is an alkyl 3-dioxolanyl-2,2-difluoro-3-hydroxypropionate of the formula



It appears that the ratio of the 3-R-hydroxy intermediate to its 3-S-hydroxy enantiomer is about 3:1. The 3-R-hydroxy enantiomer has the proper stereochemistry to yield ribose in the natural configuration, and so it is the desired enantiomeric product of the first step. The 3-R-hydroxy enantiomer can be cleanly separated from the 3-S-enantiomer by standard methods, for example by chromatography on silica gel, eluting with a solvent such as chloroform containing 0.5% methanol (v:v).

The hydroxypropionate, in either form, is hydrolyzed under very mild conditions to form the lactone form of the carbohydrate, of the formula



It has been found that proper control of the hydrolysis step will cleave the ketonide function and, unexpectedly, will also cleave the ester group, providing the lactone in a single step. The hydrolysis reagent is preferably a mildly acidic ion exchange resin, of which Dowex 50W-X12 (Dow Chemical Company) is most highly preferred. It is possible to carry out the process with other mild hydrolytic reagents, although it is possible that larger amounts of by-products may be obtained. For example, aqueous acetic acid, or other relatively strong acids such as propionic acid, formic acid, chloroacetic acid, oxalic acid and the like, may be used for the hydrolysis.

The hydroxy groups of the lactone should be protected before its keto oxygen is reduced. The usual reaction conditions are used, depending on the nature of the protecting groups which may be chosen. For example, the t-butyldimethylsilyl group is most conveniently provided in the form of its trifluoromethanesulfonate, and the protection reaction is carried out in the presence of a base such as lutidine, pyridine and the like. Acyl protecting groups such as acetyl, benzoyl and the like are provided by reacting the lactone with an acylating agent such as an acyl chloride, bromide, cyanide or azide, or with an appropriate anhydride. The reactions are conveniently carried out in a basic solvent such as pyridine, quinoline or isoquinoline, or in a tertiary amine solvent such as triethylamine, tributylamine, methylpiperidine and the like. The reaction may also be carried out in an inert solvent, to which an acid scavenger, such as a tertiary amine, has been added. Acylation catalysts such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine may be used in the reaction, if desird. The acylation reactions which provide protecting groups on the hydroxy groups are carried out at moderate temperatures in the range of from −25° to 100°. Such acylations may also be performed by acid-catalyzed reactions of the appropriate carboxylic acids, in inert organic solvents or neat. Acid catalysts such as sulfuric acid, polyphosphoric acid, methanesulfonic acid and the like are used.

Acyl protecting groups may also be provided by forming an active ester of the appropriate acid, such as the esters formed by such known reagents as dicyclohexylcarbodiimide, acylimidazoles, nitrophenols, pentachlorophenol, N-hydroxysuccinimide and 1-hydroxybenzotriazole.

Protecting groups of the ether type are placed by reacting the lactone with, for example, an appropriate diazo compound, such as diazomethane, phenyldiazomethane or a silyldiazomethane. Such reactions are commonly and effectively carried out in solvents including esters such as ethyl acetate, halogenated solvents including dichloromethane and chloroform, and ethers including diethyl ether and tetrahydrofuran. The process is usually carried out at low temperatures from about −50° to about 0°. Such etherforming reactions may also be carried out with the assistance of reagents such as trimethyloxosulfonium hydroxide, trimethylsulfonium hydroxide and trimethylselenonium hydroxide, in solvents such as dimethylsulfoxide, dimethylformamide, hexamethylphosphoramide, acetone, acetonitrile and the like.

The silyl protecting groups discussed above are placed on the hydroxy groups by the conventional methods, such as by reaction with the appropriate silylcarboxamide or bis(substituted-silyl)carboxamide, or an appropriately substituted silazane. Suitably substituted silyl methanesulfonates, toluenesulfonates and the like are also useful. An equivalent of a base is usually necessary in the reaction mixture, unless a basic solvent such as is discussed above is used as the reaction medium.

When the hydroxy groups have been protected, the keto oxygen of the lactone is reduced to the alcohol, forming the protected 2-desoxy-2,2-difluororibose or xylose of this invention. The most preferred reducing agent is diisobutyl aluminum hydride, used at a low temperature in the range of about −100° to −20°. It is necessary to carry out the reduction very carefully, in order to avoid reducing conditions so vigorous that the ring is opened at the oxygen atom. Other metal hydrides, such as the widely used lithium aluminum hydride, can also be used for the reduction, but it is necessary to keep the temperature quite low and to assure that the hydride is destroyed before the temperature is allowed to rise toward ambient. Accordingly, a solvent with a very low freezing point must be used in the reduction step. Toluene is convenient; other solvents can of course be used, including lower alkanols, especially ethanol, ethers such as diethyl ether, and the like.

An appropriate leaving group must be placed at the 1-position of the carbohydrate, in order to obtain efficient reaction with the base. The preferred leaving group is methanesulfonyl, which is readily provided by reaction with methanesulfonyl chloride in the presence of an equivalent amount of a suitable acid scavenger

such as triethylamine and the like. Other sulfonyl leaving groups are provided in the same way by reaction with the appropriate sulfonyl halide.

When a chloro or bromo leaving group is to be used, it is frequently convenient to first make the 1-acetate derivative, for instance by reaction with acetic anhydride, or another source of acetyl groups, in the presence of an equivalent or more of an acid scavenger. Then the acetate group is displaced with gaseous hydrogen bromide or hydrogen chloride, at a low temperature such as about −50° to about 0°. Since the gaseous hydrogen halide may tend to remove the protecting groups, especially silyl protecting groups, it is necessary to operate this step at quite a low temperature and to add the hydrogen halide slowly in small increments.

The bases used to form the antiviral compounds of the present invention are commonly known to organic chemists, and no discussion of their synthesis is necessary. However, the primary amino groups which are present on some of the bases should be protected before the base is coupled with the carbohydrate. The usual amino-protecting groups are used, including silyl groups such as have been discussed, as well as such typical groups as t-butoxycarbonyl, benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, formyl, acetyl, and the like.

It is often advisable to convert keto oxygen atoms on the bases to the enol form, in order to make the bases more highly aromatic and thereby allow more ready attack of the base by the carbohydrate. It is most convenient to enolize the oxygens by providing silyl protecting groups for them. The usual silyl protecting groups as discussed above are used for this purpose, also.

The reaction between the protected carbohydrate and the base is preferably carried out neat at an elevated temperature in the range of from about 50° to about 200°. It is possible, however, to use relatively high-boiling solvents for the reaction, such as dimethylformamide, dimethylacetamide, hexamethylphosphoramide and the like. However, if the coupling reaction is carried out under elevated pressure, to avoid distillation of a low-boiling solvent, any convenient inert reaction solvent can be used.

The coupling reaction may be done at low temperatures if a reaction initiator, such as a trifluoromethanesulfonyloxysilane, is used. The usual inert reaction solvents, as discussed above, may be used at temperatures in the range of from about ambient to about 100°.

The final step of the reaction sequence is the removal of the protecting groups. Most silyl protecting groups are easily cleaved by contact with water or an alcohol. The t-butyldimethylsilyl protecting group requires acid conditions, such as contact with gaseous hydrogen halide, for its removal.

Acyl protecting groups are removed by simple hydrolysis with strong or moderately strong bases, such as alkali metal hydroxides, at temperatures from about the ambient temperature to about 100°. At least one equivalent of base is needed for each protecting group, of course. Such hydrolyses are conveniently carried out in hydroxylic solvents, especially aqueous alkanols. The reactions may be also carried out, however, in any convenient solvent, such as polyols including ethylene glycol, ethers such as tetrahydrofuran and the like. ketones such as acetone and methyl ethyl ketone and other polar solvents such as dimethylsulfoxide. The cleavage of acyl protecting groups may also be performed with other bases, including, for example, sodium methoxide, potassium t-butoxide, hydrazine, hydroxylamine, ammonia, alkali metal amides and secondary amines such as diethylamine and the like. The acyl protecting groups can also be removed with acid catalysts, such as methanesulfonic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, or with acidic ion exchange resins. It is preferred to carry out such hydrolyses at a relatively high temperature, such as the reflux temperature of the mixture, but temperatures as low as ambient may be used when particularly strong acids are used.

The removal of protecting groups which are ethers is carried out by known methods, for example, with ethanethiol and aluminum chloride.

None of the reaction steps require unusual excesses of the reactants. As usual in organic syntheses, it is advisable and economical to use a moderate excess, in the range of 1.05× to 2×, for example, of the cheaper reagents to assure that the costlier ones are consumed.

The following preparations and examples further illustrate the synthesis of compounds of the present invention.

PREPARATION 1

ethyl 2,2-difluoro-3-hydroxy-3-(2,2-dimethyl- dioxolan-4-yl)propionate

To 10.2 g. of activated zinc was added a small portion of a solution consisting of 31.8 g. of ethyl bromodifluoroacetate and 22.6 g. of 4-formyl-2,2-dimethyldioxolane in 53 ml. of tetrahydrofuran and 53 ml. of diethyl ether. Care was taken to exclude water from the reaction mixture. The solution began to reflux as soon as the first addition to the activated zinc was made. The remainder of the solution was added dropwise at a rate to maintain gentle reflux throughout the addition time of about 30 minutes. The mixture was then stirred under gentle reflux for 30 minutes more. The reaction mixture was poured into 200 ml. of 1N hydrochloric acid and 200 g. of ice, and the mixture was stirred until all of the ice had melted. The aqueous mixture was then extracted four times with 70 ml. portions of diethyl ether, and the organic layers were combined and washed with 50 ml. of saturated aqueous sodium chloride and with 50 ml. of saturated aqueous sodium bicarbonate, dried over magnesium sulfate and evaporated under vacuum to obtain 26 g. of light yellow oil. The crude product was chromatographed on a 1000 g. silica gel column, eluting with chloroform containing 0.5% methanol to separate the major 3-R-hydroxy product from the minor 3-S-hydroxy product. The ratio of amounts of the two products was about 3:1; the minor product came off the column first.

Evaporation of the fractions containing the 3-R-hydroxy product provided 12.6 g. of the product in substantially pure form. It was identified by mass spectrometry, showing a fragment of weight 239, which agrees with the molecular weight of the desired product less a methyl group which was lost from the acetonide function in the spectrometric measurement. A nuclear magnetic resonance analysis of the 3-R-hydroxy product on a 90 mHz instrument in CDC13 showed features at δ=3.94–4.45 (m, 5H); 3.14 (d, J=4.5 Hz, 1H); 1.2–1.47 (m, 9H).

Analysis by the same nmr procedure of the 3-S-hydroxy product, of which 4.68 g. was obtained by evaporation of the chromatography fractions containing it, showed features at 3.75–4.47 (m, 6H); 2.95 (d, J=8 Hz, 1H); 1.25–1.5 (m, 9H).

PREPARATION 2

2-desoxy-2,2-difluoro-1-oxoribose

Fifty g. of the 3-R-hydroxy product obtained from a synthesis similar to that of Preparation 1 above was dissolved in 500 ml. of methanol and 250 ml. of water, and 250 g. of Dowex 50W-X12 resin was added. The mixture was stirred at ambient temperature for 4 days, and the mixture was then filtered through a pad of diatomaceous earth filter aid. The filtrate was evaporated to dryness under vacuum to obtain 33.0 g. of the desired product, which was identified by nmr analysis on a 90 mHz instrument in CD_3OD: δ=3.6–4.6 (series of m, 4H); 4.8 (bs, 2H).

PREPARATION 3

3,5-bis(t-butyldimethylsilyloxy)-2-desoxy-2,2-difluoro-1-oxoribose

To 13 g. of the product obtained in Preparation 2 above was added 60 ml. of dichloromethane, 22.5 ml. of 2,6-lutidine and 48.2 ml. of trifluoromethylsulfonyloxy t-butyldimethylsilane under nitrogen with mild cooling to keep the temperature below 25°. Within 15 minutes after combining the reagents, the reaction became quite exothermic and the mixture became thin and easily stirred. The mixture was stirred overnight. The mixture was diluted with 150 ml. of ethyl acetate, and was washed successively with 40 ml. of 1N hydrochloric acid, 40 ml. of saturated aqueous sodium bicarbonate and 40 ml. of saturated aqueous sodium chloride. It was then dried over magnesium sulfate and evaporated to dryness under vacuum to obtain 32.1 g. of crude product, which was chromatographed on 260 g. of 100-mesh silica gel, eluting with 10:1 (v:v) chloroform:diethyl ether. The fractions which contained the desired product were combined and evaporated under vacuum to obtain 7.8 g. of pure product. Other fractions were combined and evaporated to obtain an additional 10 g. of impure product, which was not further purified. Analysis of the pure product gave the following results: IR (neat) 1820 $cm.^{-1}$; nmr ($CDCl_3$, 90 MHz) δ=0.1–0.22 (m, 12H); 0.83–0.98 (m, 18H); 3.63–4.7 (series of m, 4H); mass spec. m/e=339=P-t-butyl.

EXAMPLE 1

3,5-bis(t-butyldimethylsilyl)-2-desoxy-2,2-difluororibose

A 10.3 g. portion of 3,5-bis(t-butyldimethylsilyloxy)-2-desoxy-2,2-difluoro-1-oxoribose, obtained from preparations similar to that of Preparation 3 above, was dissolved in 120 ml. of anhydrous toluene and cooled to −84°. To the solution was added 26 g. of diisobutyl aluminum hydride, added over a period of 20 minutes with constant stirring. The reaction mixture was held below −65° at all times. Two hours after the first addition of hydride, the reaction mixture was quenched with methanol at −20°, additional cold methanol was added until no more gassing occurred. The mixture was then allowed to warm slowly to ambient temperature, and was washed with 100 ml. of 0.1N hydrochloric acid. The aqueous layer was then washed with 100 ml. of diethyl ether, and then three times with 50 ml. portions of diethyl ether. The organic layers were combined, washed with 100 ml. of saturated aqueous sodium bicarbonate, dried over magnesium sulfate and evaporated under vacuum to dryness to obtain 8.2 g. of the desired product in crude form.

This material may be chromatographed, if necessary, on silica gel (25 g. silica/1 g. of crude product) using 100% dichloromethane for elution. nmr ($CDCl_3$, 90 MHz)δ=0.1–0.24 (m, 12H); 0.85–1.0 (m, 18H); 3.33–4.63 (series of m, 5H); 5.0–5.27 (dd, 1H); mass spec. m/e=341=P-t-butyl; $[\alpha]_D^{25°}$=+25.1°.

EXAMPLE 2

3,5-bis(t-butyldimethylsilyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose

An 0.5 g. portion of 3,5-bis(t-butyldimethylsilyloxy)-2-desoxy-2,2-difluororibose was dissolved in 5 ml. of anhydrous dichloromethane and 0.17 g. of triethylamine. To the solution was added, with mild cooling, 0.11 ml. of methanesulfonyl chloride. After three hours of stirring under nitrogen at about 25°, the mixture was evaporated under vacuum, and the residue was taken up in 10 ml. of ethyl acetate. The solution was extracted with 3 ml. of saturated aqueous sodium bicarbonate, and then successively with 3 ml. of 1N hydrochloric acid, 3 ml. of water and 3 ml. of saturated aqueous sodium chloride. The organic solution was then dried over sodium sulfate and concentrated under vacuum to obtain 0.59 g. of the desired product, nmr ($CDCl_3$, 90 MHz) δ0.05–0.16 (m, 12H); 0.78–0.90 (m, 18H); 3.0 (s, 3H); 3.63–4.59 (series of m, 4H); 5.67–5.9 (dd, 1H); mass spec. m/e=419 =P-t-butyl.

EXAMPLE 3

1-(5-methyl-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

To 2.59 g. of 3,5-bis(t-butyldimethylsiloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose was added 1.60 g. of 5-methyl-2,4-bis(trimethylsilyloxy)-pyrimidine and 45 ml. of dry 1,2-dichloroethane. To this mixture was added 1.45 g. of trifluoromethane-sulfonyloxytrimethylsilane, and the clear solution was stirred under nitrogen at reflux for about 2–3 hours. The reaction was then cooled to ambient temperature and 1.35 ml. of methanol were added and the suspension was stirred for 30 minutes. The precipitate was filtered and the filtrate was reduced to one-half its volume under vacuum and then diluted with an equal volume of dichloromethane. The solution was washed with saturated aqueous sodium bicarbonate and then with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solution was filtered and the filtrate was saturated with anhydrous hydrogen bromide. The reaction mixture was stirred for 30 minutes and was then concentrated under vacuum. The residue was dissolved in methanol and the solution was evaporated to dryness under vacuum. The residue was dissolved in water and the solution was extracted twice with diethyl ether. The water layer was then evaporated to dryness. The residue was taken up in ethanol and evaporated repeatedly to azeotrope off all water. One g. of crude product was obtained, and was chromatographed on 30 g. of Woelm silica gel (70–150 mesh), eluting with ethyl acetate to yield 0.76 g. of desired product. It was further purified by recrystallization from ethyl acetate to obtain 0.37 g. of white crystalline product. nmr (CD_3OD, 90 MHz) δ 1.93 (s, 3H); 3.5–4.67 (series of m, 4H); 4.83 (bs, 3H); 6.3 (t, J=9 Hz, 1H); 7.47 (m, 1H); mass spec. m/e=278 =Parent.

EXAMPLE 4

1-(5-methyl-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

A 5.4 g. portion of 3,5-bis(t-butyldimethylsilyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose and 5.4 g. of 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine were combined and heated under nitrogen with stirring at 100° for one hour, and then at 150° for one hour. The mixture was then cooled to ambient temperature and diluted with 25 ml. of water and 10 ml. of methanol. The slurry was filtered over a diatomaceous earth filter pad, and the cake was washed with acetone. The combined filtrate was evaporated under vacuum to obtain 5.3 g. of an oily residue. The residue was dissolved in 10 ml. of acetone and loaded on a 4.5 cm. column packed with 80 g. of silica gel. It was eluted with 15:1:1 dichloromethane:methanol:triethylamine.

The first 100 ml. of eluent was discarded, and the next 300 ml. was evaporated under vacuum to obtain 4.1 g. of syrupy crude product, which was dissolved in 40 ml. of acetone. Hydrogen chloride was bubbled through the solution for 1 hour, and then hydrogen bromide was bubbled through for 1 hour more. The solution was then evaporated at 62° to obtain 4.4 g. of oily dark product.

The above product was dissolved in 10 ml. of warm 3:1 dichloromethane:acetic acid, and loaded on a 4.5 cm. column packed with 45 g. of silica gel. The eluent used for the first 1000 ml. was 3:1 dichloromethane:acetic acid, and thereafter it was acetic acid alone. Most of the desired product was in the fractions between 1000 and 1400 ml. off the column, as determined by thin layer chromatography on silica gel using 15:1 dichloromethane:methanol. Those fractions were combined and evaporated under vacuum, and the residue was taken up in 15 ml. of cold acetone and filtered. The filtrate was stripped under vacuum to obtain an oil, which was dissolved in 5 ml. of acetone and chromatographed over 20 g. of silica gel with 15:1 dichloromethane:methanol. The product-containing fractions were combined and evaporated under vacuum to obtain 300 mg. of a semi-solid. That product was taken up in 5 ml. of acetone and filtered, and the filtrate was evaporated under vacuum to obtain 230 mg. of light brown semi-solid. It was dissolved in 10 ml. of saturated aqueous sodium bicarbonate, and the solution was extracted twice with 15 ml. portions of diethyl ether. The aqueous phase was then evaporated under vacuum, the residue was slurried in acetone and filtered, and the filtrate was evaporated under vacuum to obtain 140 mg. of the desired product as a tan viscous oil.

The following example illustrates a preferred method of isolating a compound of the present invention.

EXAMPLE 5

1-(5-methyl-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

To 80.0 g. of 3,5-bis(t-butyldimethylsilyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose under a nitrogen atmosphere was added 1.4 1. of freshly distilled methylene chloride and 49.5 g. of 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine. To this mixture was added 44.8 g. of trifluoromethanesulfonyloxytrimethylsilane and the reaction mixture was refluxed for approximately 3½ hours. The reaction mixture was stirred at room temperature overnight and 41.6 ml. of methanol was added thereto. The resulting mixture was stirred for approximately 30 minutes and the precipitated solid was collected by filtration. The filtrate was concentrated under vacuum at 45° to provide a dark oil which was dissolved in 500 ml. of methylene chloride saturated with anhydrous hydrogen bromide. The resulting suspension was stirred for approximately 3 hours after which the volatiles were removed under vacuum at 45°. The residue was dissolved in 100 ml. of 10% sodium bicarbonate and 100 ml of diethyl ether. The aqueous layer was separated and concentrated in vacuo at 50° to provide a residue which was triturated three times with 100 ml. portions of hot ethyl acetate. The organic layers were combined and evaporated under vacuum at 45° to provide a residue which was dissolved in 50 ml. of water. This solution was chromatographed in 10 ml. portions on a Waters Prep 500 C^{18} reverse phase column using water/methanol (v:v, 9:1) as the eluent to provide 2.21 g. of 1-(5-methyl-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose. nmr (CD_3OD, 90 MHz) δ 1.9 (s, 3H), 3.65–4.65 (m, 4H), 4.83 (s, 3H), 6.12 (dd, J=7 Hz, 12 Hz, 1H), 7.70 (s, 1); mass spec. m/e=278 =p.

EXAMPLE 6

1-(5-iodo-2-oxo-4-amino-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

To a solution of 1.99 g. of 3,5-bis(t-butyldimethylsilyloxy)-1-methanesulfonyloxy-2-desoxy-2,2difluororibose in 35 ml. of dry methylene chloride under a nitrogen atmosphere was added 2.08 g. of tris (trimethylsilyl)-5-iodocytosine and 1.11 g. of trifluoromethanesulfonyloxytri The reaction mixture was refluxed for approximately 16 hours and cooled to room temperature. Five milliliters of methanol were added to the mixture which was stirred for approximately 30 minutes. The precipitated solid was collected by filtration and the filtrate was evaporated to dryness under vacuum. The residue was dissolved in 20 ml. of methylene chloride saturated with anhydrous hydrogen bromide to provide a suspension which was stirred for approximately 3 hours at room temperature. The volatiles were evaporated under reduced pressure at 45° and the resulting residue was dissolved in 15 ml. of water. The solution was neutralized to a pH of approximately 7 to 8 with 10% sodium bicarbonate and washed one time with 10 ml. of ethyl acetate. The aqueous layer was chromatographed on a Whatman Prep ODS-3 reverse phase column in 2 ml. portions employing water/methanol (v:v, 9:1) as the eluent to provide 30 mg. of 1-(5-iodo-2-oxo-4-amino-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose nmr (CD_3OD, 90 MHz) 6 3.47-4.66 (m, 4H), 4.78 (s, 4H), 6.14 (2e, J=7Hz, 1H), 8.32 (s, 1H); mass spec. m/e=389 =p.

EXAMPLE 7

1-(5-fluoro-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

A solution of 1.1 g. of 3,5-bis(t-butyldimethylsilyloxy)-1-methanesulfonyloxy-2-desoxy-2,2difluororibose, 0.83 g. of 5-fluoro-2,4-bis(trimethylsilyloxy)pyrimidine, and 0.655 g. of trifluoromethanesulfonyloxytrimethylsilane in 20 ml. of methylene chloride was refluxed for approximately 17 hours under nitrogen. The reaction mixture was cooled to room temperature and 3 ml. of methanol was added thereto. The resulting solution was stirred for approximately 30 minutes at room tempera-

ture and the precipitated solid was collected by filtration. The filtrate was evaporated to dryness under vacuum at 50° and the residue was dissolved in 15 ml. of methylene chloride saturated with anhydrous hydrogen bromide. The resulting suspension was stirred for approximately 30 minutes and the volatiles were removed in vacuo at 45° . The residue was dissolved in 15 ml. of water and the aqueous solution was extracted one time with 10 ml. of ethyl acetate. The aqueous layer was neutralized with sodium carbonate to a pH of approximately 7 and the solution was evaporated to dryness in vacuo at 50°. The residue was dissolved in about 6 ml. of water and the resulting solution was chromatographed in 2 ml. portions on a Whatman ODS-3 50 cm reverse-phase column using water as the eluent to provide 30 mg. of 1-(5-fluoro-2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluorori (CD_3OD, 90 MHz) δ 3.63–4.6 (m, 4H), 4.79 (s, 3H), 6.04 (t, J=7 Hz, 1H), 8.07 (d, J=6 Hz, 1H); mass spec. m/e=282 =p.

EXAMPLE 8

1-(2-oxo-4-amino-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

Under nitrogen, to a solution of 47.3 g. of 3,5-bis(t-butyldimethylsilyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose in 940 ml. of methylene chloride was added 48 g. of bis(trimethylsilyl)-N-acetylcytosine. To this mixture was added 39.23 g. of trifluoromethanesulfonyloxytrimethylsilane and the resulting mixture was stirred under reflux for approximately 15 hours. The reaction mixture was cooled to room temperature and 16 ml. of methanol was added thereto. The resulting solution was stirred for approximately 30 minutes and concentrated to about one-half of its original volume. The solution was cooled in ice and the precipitated solid was collected by filtration. The filtrate was shaken one time with approximately 300 ml. of 10% sodium bicarbonate and one time with 100 ml. of brine. The organic layer was evaporated to dryness in vacuo at 45° and the residue was dissolved in 1.3 1. of methanol saturated with ammonia. The resulting suspension was allowed to stir overnight at room temperature and the volatiles were removed under vacuum at 45°. The residue was dissolved in 275 ml. of methanol and 100 g. of Bio Rad ion exchange resin (AG 50WX8) was added thereto. The suspension was stirred at room temperature overnight and the resin was collected by filtration. The resin was rinsed with 100 ml. of methanol and suspended in 100 ml. methanol and 50 ml. of concentrated ammonium hydroxide. The resin containing suspension was stirred vigorously for 15 minutes and the resin was collected by filtration. This procedure was twice repeated with additional ammonia saturated methanol. The basic methanolic filtrates were combined and evaporated at 45° under vacuum to provide 13.8 g. of a solid. This material was chromatographed on a Waters Prep 500 C^{18} Reverse Phase Column with water as the eluent to provide 1.26 g. of 1-(2-oxo-4-amino-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose. nmr (CD_3OD, 90 MHz) δ 3.7–4.65 (m, 4H), 4.83 (s, 4H), 5.97 (d, J=8 Hz, 1H), 6.24 (t, J=7 Hz, 1H), 7.88 (d, J=8 Hz, 1H); mass spec. m/e=263 =p.

EXAMPLE 9

1-(2-oxo-4-amino-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluoroxylose

Under nitrogen, to 23 g. of 3,5-bis(t-butyldimethylsilyloxy)-1-methanesulfonyloxy-2-desoxy-2,2difluoroxylose was added 23 g. of tris(trimethylsilyl)cytosine and 300 ml. of methylene chloride. To this mixture was added 10.84 g. of trifluoromethanesulfonyloxytrimethylsilane and the mixture was refluxed for approximately 16 hours. The mixture was cooled to room temperature and 20 ml. of methanol was added thereto. The solution was stirred vigorously for approximately 1 hour at room temperature and the precipitated solid was collected by filtration. One hundred milliliters of water were added to the organic layer and the suspension was stirred vigorously for 30 minutes. The organic layer was separated and evaporated to dryness under reduced pressure to provide 11.2 g. of a brown oil. The residue was dissolved in 97 ml. of methanol to which 33 g. of Bio Rad AG 50X8 cationic exchange resin was added. The suspension was stirred for approximately 16 hours at room temperature and the resin was collected by filtration. The resin was washed with 50 ml. of methanol and stirred vigorously in a solution of 100 ml. of methanol and 100 ml. of ammonium hydroxide. This procedure was twice repeated and the combined filtrates were concentrated under vacuum at 50° to provide 2.09 g. of a yellow residue. The residue was suspended in 25 ml. of water and stirred vigorously for 15 minutes. The insoluble precipitate was collected by filtration to provide 0.25 g. of a substance labelled Compound A. The filtrate was concentrated in vacuo at 50° to provide 0.86 g. of a compound labelled B. Compound A was dissolved in 20 ml. of methanol and stirred for 3 days with Bio Rad AG 50WX8 at ambient temperature. The resin was filtered and slurried in 30 ml. of a 1:1, v:v solution of methanol/ammonium hydroxide. The resin was again filtered and the filtrate was concentrated in vacuo at 50° to provide 0.14 g. of 1-(2-deoxy-2,2-difluoro-β-D-xylofuranosyl)cytosine. nmr (CD_3OD, 90 MHz) δ 3.72–4.34 (s, 4H), 5.86 (d, J=8 Hz, 1H), 6.17 (d, J=15 Hz, 1H), 7.78 (d, J=8 Hz, 1H); mass spec. m/e=263 =p.

The compound labelled B was chromatographed on a Whatman 50 cm ODS-3 Reverse Phase Prep column using water/methanol (v:v, 1:1) as the eluent to provide 0.06 g. of 1-(2-deoxy-2,2-difluoro-α-d-xylofuranosyl)-cytosine. nmr (CDO_3D, 90 MHz)δ 6 3.53–3.9 (m, 2H), 4.1–4.57 (m, 2H) 4.83 (s, 4H), 5.9 (d, (dd, J=7 Hz, 12 Hz, 1H) 7.55 (d, J=8 Hz, 1H); mass spec. m/e=263 =p.

EXAMPLE 10

1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

A solution of 0.19 g. of 1-(2-oxo-4-amino-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose in of glacial acetic acid and 4 ml. of water was refluxed for approximately 24 hours. The reaction mixture was cooled to ambient temperature and the volatiles were removed under vacuum at a temperature in the range of about 60° to about 70°. The residue was evaporated several times with 5 ml. of toluene. The residue was dissolved in 12 ml. of methanol and the resulting solution was cooled in a salt/ice bath to approximately −15°. The solution was saturated with anhydrous ammonia and allowed to stir overnight at room temperature. The volatiles were evaporated under reduced pressure at 45° and the residue was suspended in 5 ml. of hot water. The insoluble material was collected by filtration and the filtrate was chromatographed on a Whatman 50 cm Partisil ODS-3

Reverse Phase column using water/methanol (v:v, 9:1) as the eluent to provide 0.05 g. of the product containing a small trace of unreacted starting material. This unreacted starting material was removed by passing a solution of the solid in approximately 5 ml. of methylene chloride containing 10% methanol by volume through a Waters Silica Sep-Pak. The eluent was evaporated in vacuo at 45° to provide 0.036 g. of 1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose. nmr (CD_3OD, 90 MHz) δ 3.54–4.48 (m, 4H), 4.83 (s, 3H), 5.69 (d, J=8 Hz, 1H), 6.10 (dd, J=7 Hz, 9 Hz, 1H), 7.8 (d, J=8 Hz, 1H); mass spec. m/e=264 =p.

EXAMPLE 11

1-(5-methyl-2-oxo-4-amino-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose

Under nitrogen, a solution of 1.86 g. of 3,5-bis(t-butyldimethylsilyloxy)-1-methanesulfonyloxy-2-desoxy-2,2-difluororibose, 1.87 g. of tris(trimethylsilyl) cytosine and 1.34 g. of trifluoromethanesulfonyloxytrimethylsilane in 37 ml. of dry methylene chloride was refluxed overnight. The reaction mixture was cooled to room temperature and 1 ml. of methanol was added thereto. The precipitated solid was collected by filtration and the filtrate was evaporated under vacuum at 45°. The residue was dissolved in approximately 20 ml. of water and this solution was concentrated to approximately one-half of its original volume by evaporation under vacuum at 50°. The precipitate that formed was collected by vacuum filtration and the filtrate was evaporated in vacuo at 50°. The residue was triturated several times with 10 ml. portions of warm acetone. The organic extracts were combined and evaporated in vacuo at 45° to provide 1.67 g. of a yellow oil. This material was dissolved in 15 ml. of methanol/water (v:v, 2:1) and stirred overnight with 5 g. of Bio Rad AG 50WX8. The suspension was saturated with anhydrous ammonia and stirred for approximately 10 minutes. The resin was collected by vacuum filtration and suspended in 30 ml. of methanol/ammonia (1:1, v:v). The suspension was stirred for approximately 10 minutes. The resin was collected by filtration and the basic filtrates were combined and concentrated under vacuum at 50° to provide 1.5 g. of an orange oil. The oil was dissolved in 10 ml. of water and this solution was chromatographed in 2 ml. portions on a Whatman Partisil ODS-3 50 cm Reverse Phase Prep column using water as the eluent to provide 0.07 g. of 1-(5-methyl-2-oxo-4-amino-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose. nmr (CD_3OD, 90 MHz) δ 1.94 (s, 3H), 3.53–4.62 (m, 4H), 4.75 (s, 4H), 6.17 (t, J=8 Hz, 1H), 7.67 (s, 1H); mass spec. m/e=277 =p.

In addition to the antiviral utility of the present compounds, certain of the compounds of the present invention have also demonstrated excellent oncolytic activity in standard cancer screens. A particularly preferred compound with this utility is the compound of Example 8, 1-(2-oxo-4-amino-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose. This compound demonstrated activity in tumor systems L1210V lymphocytic leukemia, 6C3HED lymphosarcoma, CA-755 adenocarcinoma, P1534J lymphatic leukemia and X5563 plasma cell myeloma. When used for cancer chemotherapy, dosages per day of the active compounds will be in the range of about 0.1 to about 1200 mg./kg. of body weight. In the treatment of adult humans, the range of about 0.1 to about 50 mg./kg., in single or divided doses, is preferred.

The antiviral effect of the compounds of this invention has been shown by a proven in vitro test, which was carried out as follows. A representative compound, that of Examples 3 and 4 above, was tested, and is referred to in the following description by the code term "DFAT".

TEST 1

African green monkey kidney cells (BSC-1) were grown in 25 cm.2 Falcon flasks at 37° in medium 199 with 5 percent inactivated fetal bovine serum (FBS), penicillin (150 units/ml.) and streptomycin (150 mcg./ml.). When confluent monolayers were formed, the supernatant growth medium was removed and 0.3 ml. of an appropriate dilution of pseudorabies virus or *Herpes simplex* virus, type I, was added to each flask. After adsorption for one hour at room temperature, the virus infected cell sheet was overlaid with a medium comprising one part 1 percent Ionagar No. 2 and one part double strength medium 199 with FCS (fetal calf serum), penicillin, and streptomycin and also containing crude DFAT at concentrations ranging from 100 to 0.39 micrograms per milliliter (mcg./ml.). A flask containing no DFAT served as a control. The stock solution of DFAT was made up in dimethylsulfoxide at a concentration of 104 mcg./ml. The flasks were incubated for 72 hours at 37°. Plaques were seen in those areas where the virus infected and reproduced in the cells. A solution of 10 percent formalin and 2 percent sodium acetate was added to each flask to inactivate the virus and fix the cell sheet to the surface of the flask. The virus plaques, irrespective of size, were counted after staining the surrounding cell areas with crystal violet. The plaque count was compared to the control count at each drug concentration. The activity of the compound was expressed as percentage plaque inhibition.

The results of these evaluations are reported below in Tables 1 and 2.

TABLE 1

Percent Plaque Inhibition at Specified Mcg./Ml. of DFAT Concentration in Agar Overlay								
Herpes simplex, type I								
100	50	25	12.5	6.25	3.12	1.56	0.78	0.39
96%	72%	53%	35%	15%	12%	0	8%	4%

TABLE 2

Percent Plaque Inhibition at Specified Mcg./Ml. of DFAT Concentration in Agar Overlay						
	Pseudorabies Virus					
	100	50	25	12	6	3
DFAT	23%	18%	15%	12%	6%	5%

The antiviral nucleosides of the present invention are used for the treatment of viral infections in the manner usual in the treatment of such pathologies. The compounds are effective for the treatment of viral infections in general, and most particularly in the treatment of infections caused by viruses of the herpes genus.

The compounds are effectively administered orally, topically or parenterally. In general, dosage rates in the range of from about 5 mg./kg. to about 500 mg./kg. are useful. It is more preferred to administer rates in the range of from about 10 mg./kg. to about 100 mg./kg.

The compounds are usually used in medicine in the form of one of the pharmaceutical compositions of the

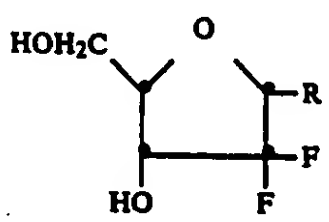
present invention, which compositions are novel and important because of the presence of the novel nucleosides in them. The formulation of the compositions is conventional, and follows the usual practices of pharmaceutical chemists. When a nucleoside of the present invention is to be administered topically, it is formulated as a topical composition, such as a cream or ointment to be rubbed into the affected tissue. Creams are emulsions of an oily phase and an aqueous phase, in which the nucleoside is dissolved or suspended. Ointments are greasy or waxy compositions, in which the nucleoside may be soluble but may be suspended, if it is insoluble at the desired concentration.

Parenteral compositions are preferably formulated in such a way that the nucleoside can be dissolved for injection, but most of the nucleosides are by no means highly water-soluble. Thus, it is more common for a parenteral product to be formulated as a dried powder of the nucleoside and physiologically-acceptable suspending agents, such as starch, sugar and the like, to which sterilized water is added to form a suspension to be injected. Parenteral compositions can be formulated in aqueous bases containing moderate amounts of physiologically-acceptable solvents, such as propylene glycol and the like, and such compositions may be capable of dissolving the present nucleosides at acceptable concentrations.

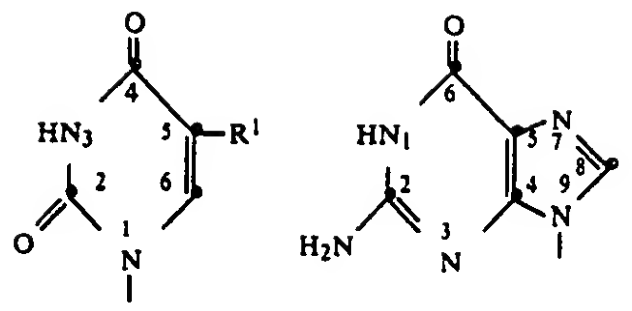
A great many types of orally administered compositions are in common use, including unit dosage forms such as tablets and capsules, and liquid dosage forms such as suspensions. In general, unit dosage forms are preferred in pharmacy and are formulated in such a way as to provide the usual dose in one or a small number of tablets or capsules. The formulation of tablets, making use of appropriate lubricants, binding agents and disintegration agents, is and long has been thoroughly understood by pharmaceutical chemists. The formulation of capsules involves only the dilution of the nucleoside with an appropriate proportion of an inert powdery substance, such as lactose, to provide the proper bulk to fill the desired size of capsule. The formulation of orally-administered suspensions is carried out by finely grinding the nucleoside, and intimately mixing it with a comparatively viscous aqueous-base liquid. The viscosity is adjusted by the addition of pharmaceutically-acceptable thickening or gel-forming agents including vegetable gums, chemically-modified cellulose derivatives and the like. Of course, appropriate flavors are used to make the suspensions organoleptically acceptable.

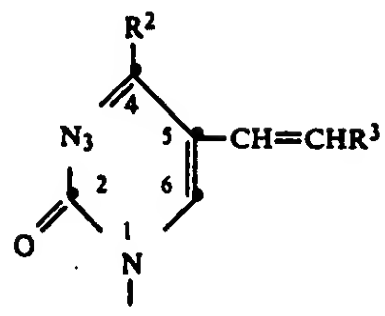
I claim:

1. A nucleoside of the formula



wherein R is a base selected from the group consisting of





wherein

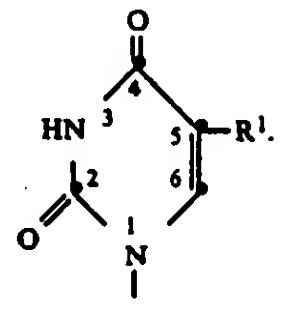
R^1 is hydrogen, methyl, bromo, fluoro, chloro or iodo;

R^2 is hydroxy;

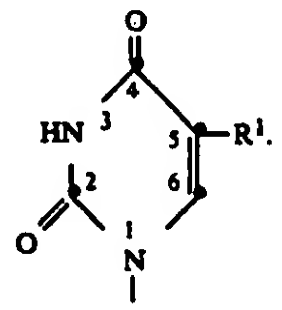
R^3 is hydrogen, bromo, chloro or iodo.

2. A nucleoside of claim 1 wherein the carbohydrate moiety is in the ribose form.

3. A nucleoside of claim 2 wherein the base is of the formula



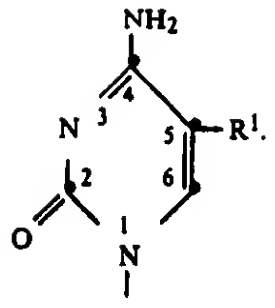
4. A nucleoside of claim 1 wherein the base is of the formula



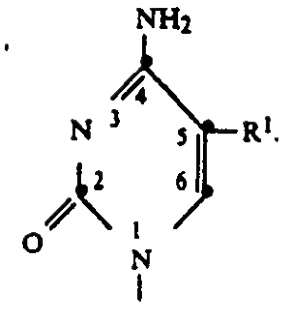
5. A nucleoside of claim 4 wherein R^1 is methyl.

6. A nucleoside of claim 3 wherein R^1 is methyl.

7. A nucleoside of claim 1 wherein the base is of the formula



8. A nucleoside of claim 2 wherein the base is of the formula



9. A nucleoside of claim 7 wherein R^1 is iodo.

10. A nucleoside of claim 8 wherein R^1 is iodo.

11. A nucleoside of claim 7 wherein R^1 is hydrogen.

12. A nucleoside of claim 8 wherein R^1 is hydrogen.

13. A method of treating Herpes viral infections in mammals comprising administering to a mammal in need of such treatment an anti-Herpes viral effective amount of a compound of claim 1.

14. A pharmaceutical composition useful for treating Herpes viral infections comprising an anti-Herpes viral effective amount of a compound of claim 1 and a pharmaceutically-acceptable carrier, diluent or excipient therefor.

* * * * *

EXHIBIT III

A) Certificate of Correction for U.S. Patent No. 4,808,614; and

B) Receipt for Maintenance Fee Payment Made in 1992.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,808,614

DATED : February 28, 1989

INVENTOR(S) : Larry W. Hertel

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2, line 47 "R" in the structure should read -- =O --

Column 3, line 8 should be a new paragraph.

Column 4, line 3 should read -- 1-[4-amino-5-(2-chlorovinyl)-2-oxo-1H-pyrimidin-1-yl]-2-desoxy-2,2-difluororibose

Column 10, line 61 "CDC13" should read -- $CDCl_3$ --

Column 14, line 21, "s, 1)" should read -- (s,1H) --

Column 14, line 33 "thanesulfonyloxytri" should read -- thanesulfonyloxytrimethylsilane --

Column 14, line 52 "CD_3OD, $90MH_z$) 6" should read -- (CD_3OD, $90MH_z$)δ ---

Column 15, line 17 "-2,2-difluorori (CD_3OD ..." should read -- -2,2-difluororibose. nmr (CD_3OD ... --

Column 16, line 37 "MH_z)δ3.72-4.34 (s,4H)" should read -- MH_z)δ3.72-4.34 (m,4H), 4.78 (s,4H) --

Column 16, in line 44 delete the figure 6.

Column 16, line 45, insert after "(d," -- J=8 Hz, 1H), 6.3 --

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,808,614

DATED : February 28, 1989

INVENTOR(S) : Larry W. Hertel

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16, line 52 insert -- 16 ml -- after "in"

Signed and Sealed this

Twentieth Day of February, 1990

Attest:

Priscilla R. Fuller

Attesting Officer

JEFFREY M. SAMUELS

Acting Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

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UNITED STATES PATENT AND TRADEMARK OFFICE

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Twentieth Day of February, 1990

Attest:

JEFFREY M. SAMUELS

Attesting Officer *Acting Commissioner of Patents and Trademarks*

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

ELI LILLY AND COMPANY
ATTENTION: PATENT DIVISION
LILLY CORPORATE CENTER
INDIANAPOLIS, IN 46285

DATE MAILED
08/03/92

243535

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,808,614	183	900	----	07/058,219	02/28/89	06/04/87	05	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	X-5707B

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

EXHIBIT IV

Notice of Claimed Investigational Exemption for a New Drug

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No. 0910-0014

3

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

NOTE: No drug may be shipped or study initiated unless a complete statement has been received. *(21 CFR 312.1(a)(2)).*

Name of Sponsor Eli Lilly and Company Date January 28, 1987

Address Lilly Corporate Center
Indianapolis, Indiana 46285 Telephone ( ) see page 2

Name of Investigational Drug Vials Compound LY188011 Hydrochloride

FOR A DRUG:

Food And Drug Administration
Office of New Drug Evaluation *(HFN-106)*
5600 Fishers Lane
Rockville, Maryland 20857

FOR A BIOLOGIC:

Food and Drug Administration
Office of Biologics *(HFN-823)*
8800 Rockville Pike
Bethesda, Maryland 20205

Dear Sir:

The sponsor, Eli Lilly and Company, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 312.1 of Title 21 of the Code of Federal Regulations.

Attached hereto in triplicate are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, or each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

7. A total (one in each of the three copies of the notice) of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to under-

take the phase of the investigation outlined in section 10 of the "Notice of Claimed Investigational Exemption for a New Drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed Form FD-1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations and a description of the institutional review committee, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase I starts when the new drug is first introduced into man - only animal and in vitro data are available - with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies. If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

c. Institutional review board (IRB). The sponsor must give assurance that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The sponsor must also provide assurance that the investigators will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that the investigators will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazard to the human subjects. FDA will regard the signing of the Form FDA-1571 as providing the necessary assurances above.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. A limitation on an exemption does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11. A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. A statement that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver; and for investigations subject to institutional review committee approval as described in item 10c above, and additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

15. When requested by the agency, an environmental impact analysis report pursuant to § 25.1 of this chapter.

16. A statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies have not been conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in conducting the study and those required in the regulations.

Very truly yours,

SPONOR

ELI LILLY AND COMPANY

PER

INDICATE AUTHORITY

M. W. Talbott, Ph.D., Regulatory Advisor

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

EXHIBIT V

FDA Receipt Letter for
Notice of Claimed Investigational
Exemption for a New Drug

FEB = 1987 M.W.T.

1383.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 3 1987

IND 29,653

Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, Indiana 46285

Attention: M.W. Talbot, Ph.D.
Regulatory Advisor
Clinical Investigation
and Regulatory Affairs

Dear Sir/Madam:

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 29,653

Sponsor: Eli Lilly and Company

Name of Drug: Compound LY188011 Hydrochloride

Date of Submission: January 28,1987

Date of Receipt: February 2, 1987

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

U.S. GOVERNMENT PRINTING OFFICE: 1984 - 436-677/7217

Should you have any questions concerning this IND, please call:

Ms. Cathie Schumaker
Consumer Safety Officer
(301) 443- 5197

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
National Center for Drugs and Biologics(HFN-150)
Attention: DOCUMENT CONTROL ROOM # ~~17B-28~~ 9B23
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Cathie Schumaker, Jr

Director
Division of Oncology and Radiopharmaceutical
Drug Products
National Center for Drugs and Biologics

CC:
Orig. File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228f (6/83)

cc: Dr. R. A. Browne
Mr. R. A. Conrad
Dr. A. Dinner
Mr. J. M. Fose
Dr. W. W. Hargrove
Ms. L. J. Heid
Mr. T. L. Jeatran
Dr. D. W. Johnson
Dr. J. H. Marsden
•Dr. M. E. Ross
Dr. W. L. Thompson
Dr. A. J. Weinstein

January 28, 1987

Food and Drug Administration
Center for Drugs and Biologics
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, Maryland 20852

Gentlemen:

Re: Vials Compound LY188011 Hydrochloride (Oncolytic Agent)

Accompanying this letter is Form FD 1571 information supporting Phase I-II studies of Compound LY188011 as an oncolytic agent.

Section 10(a) contains Protocol B9E MC JHAC for the initial dose-ranging and pharmacology study in adult patients with advanced or metastatic cancer. This study will be conducted by Dr. Martin N. Raber. A Form FD 1573 and curricula vitae for him and his assisting physicians are provided in Section 9.

The dosage selected for the first clinical trial, 20 mg/m^2 administered once a week, is based on the acute toxicology in the mouse (Studies M-V-24-86 and M-V-25-86) and rat (R-V-24-86), and the chronic (90 day) toxicology in the dog (D05086) and the mouse (M01586).

Two features of these chronic toxicology studies are worthy of comment. First, the observed toxicity was extremely schedule dependent. The chronic toxicology experiments studied several different regimens, all of which may ultimately be examined in man. The decision regarding the dosage in man was based, however, on the comparable clinical schedule. Second, the toxicologists refer in their summaries to a minimal toxic dose level. This should not be confused with the concept of a toxic low dose. The minimal toxic dose level referred to in these studies specifically refers to the once a week schedule, and implies the level at which clinically significant toxicity is seen in that animal species. The minimal toxic dose level does not refer to the lowest dose at which any biologic activity is seen.

In the acute toxicology (single dose) studies, the LD_{10} and LD_{50} in mice were greater than 2.5 g/m^2. In the rat, the LD_{10} was approximately 200 mg/m^2, and the LD_{50} 400 mg/m^2. The dosage chosen for the clinical trial, 20 mg/m^2 once a week, is 10% of the LD_{10} in the rat and approximately 2% of the LD_{10} in the mouse, based on the acute toxicology experiments. In the chronic toxicology experiments in the dog, mild (but statistically significant) depression of the WBC was seen on 30 mg/m^2 twice a week (60 mg/m^2 total per week), three times the postulated started dose. In the mouse, mild changes were also seen in both the red cell series and in the white cell series, at a dose of 120 mg/m^2 weekly or 60 mg/m^2 twice weekly.

Although much lower doses produced toxicity in animals when Compound LY188011 was administered on a chronic daily schedule, we feel the starting dose chosen is the appropriate one based on comparable animal schedules.

Dr. Michael E. Ross will be the monitor for clinical trials conducted under this IND. His curriculum vitae is also included in Section 9.

Very truly yours,

ELI LILLY AND COMPANY

M. W. Talbott, Ph.D.
Regulatory Advisor
Clinical Investigation
and Regulatory Affairs

MWT:lm
Enclosure

THIS DOCUMENT CONTAINS TRADE SECRETS, OR COMMERCIAL OR FINANCIAL INFORMATION, PRIVILEGED OR CONFIDENTIAL, DELIVERED IN CONFIDENCE AND RELIANCE THAT SUCH INFORMATION WILL NOT BE MADE AVAILABLE TO THE PUBLIC WITHOUT THE EXPRESS WRITTEN CONSENT OF ELI LILLY AND COMPANY.

AMENDMENTS AND SUPPLEMENTS TO THIS DOCUMENT MAY CONTAIN TRADE SECRETS, OR COMMERCIAL OR FINANCIAL INFORMATION, PRIVILEGED OR CONFIDENTIAL, DELIVERED IN CONFIDENCE AND IN RELIANCE THAT SUCH INFORMATION WILL NOT BE MADE AVAILABLE TO THE PUBLIC WITHOUT THE EXPRESS WRITTEN CONSENT OF ELI LILLY AND COMPANY.

To the Reviewers:

To co-ordinate our activities with yours, we suggest that any wires or written communications, regardless of subject, concerning this file be directed to:

M. W. Talbott, Ph.D.
Regulatory Advisor
Clinical Investigation and Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, Indiana 46285

Any telephone calls relating to manufacturing-controls should be made to:

Dr. A. Dinner 276-3709*

or in his absence to:

Mr. J. M. Fose 276-4498*

Any calls relating to toxicology-pharmacology should be made to the Greenfield Laboratories of Eli Lilly and Company to:

Dr. M. E. Amundson 467-4301*

or in his absence to:

Dr. E. C. Pierce 467-4315*

Any calls dealing with clinical reports or with labels and literature should be made to Dr. Talbott between 7:30 a.m. and 4:15 p.m. (EST).

Dr. M. W. Talbott 276-2574*
846-2345* (Home)

or in his absence to:

Dr. Robert A. Browne 276-6626*
841-0601* (Home)

* Area Code 317

On holidays, Saturdays, or Sundays, call the above personnel at home using the telephone numbers indicated.

By way of explanation, Dr. Dinner and Mr. Fose are in the Development Division; Drs. Amundson and Pierce are in the Toxicology Division; and Drs. Talbott and Browne are in the Medical component. It is through Dr. Talbott's office that FDA submissions for this file are made.

Close liaison among the three divisions will result in any messages, no matter how received, being brought to the attention of all concerned.

W. L. Thompson, M.D.

lm

1533.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 29,653

JUN 1 5 1987

Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, Indiana 46285

Attention: M.W. Talbott, Ph.D.
Regulatory Advisor
Medical Regulatory Affairs

Dear Dr. Talbott:

Reference is made to your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Compound LY188011 Hydrochloride (oncolytic agent).

We also acknowledge receipt of your amendments dated April 13 and May 18, 1987.

Reference is also made to the May 12, 1987 telephone conversation between Ms. Sue Warthen of Eli Lilly and Ms. Cathie Schumaker of this Administration in which notification was given that the "clinical hold" of your IND has been removed and it is considered reasonably safe to proceed with the studies as amended. However, we have the following requests and recommendations:

1. The informed consent should be modified to state that fertile males should use adequate contraception if sexually active.

2. Section E-2 should include explicit instructions for reconstitution and use of the drug.

The following manufacturing and control issues may be addressed at a later date, but before Phase III studies are initiated:

1. The pH for the drug product, placebo and diluting solution should be specified. Please amend the submission by including this information in the Composition Statements, Batch Formulas and Manufacturing Instructions. The 2.5-7.0 pH range specified in the controls for the new drug is too broad and it is recommended that it be narrowed.

MWT JUN 22 '87

2. A detailed description of the synthesis process should be submitted, including in-process controls and possible by-products. Yields should be stated. It is recommended that pivotal intermediates be subjected to rigid specifications to avoid undetected impurities and batch-to-batch variations.

3. The source and purity of all materials used in the synthesis should be stated and specifications provided for their acceptance.

4. Possible impurities and decomposition products of the drug substance and drug product should be identified and their levels in several batches reported.

5. Methods validation should be provided for Method WGZ-O for the determination of related substances.

6. A full description should be submitted of the method of manufacture for the drug product, placebo and diluting solution; including amounts of ingredients, operating conditions, description of equipment and in-process controls.

7. The containers and closures should be described in full detail and acceptance specifications should be provided. The aluminum seals should also be included in the description of the container-closure system.

8. The laboratory controls for the drug product should be revised by including specifications and suitable test methodology for impurities and decomposition products.

9. It is recommended that specifications should be established for the reconstituted solution of the drug; including clarity and completeness of solution, pH, potency, impurities and decomposition products and sterility. The stability testing protocol should also include these tests.

10. The stability data for the drug substance, drug product and reconstituted solution of the drug should be reported to the FDA as they become available in support of the proposed expiration dating period.

11. Draft labels should be submitted for the placebo and diluting solution.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and regulations. This includes the immediate reporting of any alarming reactions, an agreement to provide for any significant changes in your clinical protocol by means of an amendment and the submission of progress reports detailing the course of your study at intervals not to exceed one year.

Sincerely yours,

John F Palmer

John F. Palmer, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

December 22, 1994

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20852

Re: NDA 20-509 - Gemzar® (gemcitabine hydrochloride)
Pre-submission of chemistry, manufacturing and control data and nonclinical pharmacology and toxicology data

This letter accompanies a pre-submission of an original New Drug Application for Gemzar (gemcitabine hydrochloride). This document includes the chemistry, manufacturing, and control data and the nonclinical pharmacology and toxicology data. The remaining sections of the NDA are anticipated to be submitted by February, 1995. We understand that a User Fee is not due with this pre-submission, nor is any review clock initiated until the entire application is submitted and filed.

Gemzar is a new intravenous oncolytic agent being submitted for the indication of pancreatic cancer. This application is formatted and organized according to 21 CFR § 314.50 and follows the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications".

To co-ordinate our activities with yours, we suggest that any written communications, regardless of subject, concerning this application be directed to:

M.W. Talbott, Ph. D.
Director, Worldwide Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, Indiana 46285

Telephone calls or faxes, regardless of subject, should be made to:

Dr. Kelly Freeman
Regulatory Scientist
North American Regulatory Affairs
317-276-1337
317-823-4082 (home)
FAX number: 317-276-1652

or in her absence to:

Dr. Timothy Franson
Executive Director
North American Regulatory Affairs
317-277-1324
317-873-0592 (home)

Any telephone calls related to manufacturing and control issues should be made to:

Dr. Gregory Davis
Director, Regulatory Affairs,
Chemistry, Manufacturing and Control
317-276-4125

or in his absence to:

Dr. Richard Raths
Head, Regulatory Affairs,
Chemistry, Manufacturing and Control
317-276-4248

Any calls relating to toxicology or pharmacology issues should be made to

Dr. Douglas Morton
Vice President, Toxicology
317-277-4301

or in his absence to:

Dr. Homer Pearce
Vice President, Cancer Research
317-276-6349

On holidays, Saturdays, or Sundays, call Dr. Freeman or Dr. Franson at home using the telephone numbers indicated. Close liaison between the Lilly personnel will result in any messages, no matter how received, being brought to the attention of all concerned.

Please call Dr. Kelly Freeman at 317-276-1337 or me at 317-276-2574 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

M.W. Talbott, Ph.D.
Director
Worldwide Regulatory Affairs

Enc.

cc: Ms. Linda McCollum (cover letter only)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1991
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT
Eli Lilly and Company

ADDRESS *(Number, Street, City, State and Zip Code)*
Lilly Corporate Center
Indianapolis, IN 46285

DATE OF SUBMISSION
December 22, 1994

TELEPHONE NO. *(Include Area Code)*
(317) 276-2000

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
20-509

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Gemcitabine

PROPRIETARY NAME *(If any)*
Gemzar

CODE NAME *(If any)*
LY264368

CHEMICAL NAME
2'-deoxy-2',2'-difluorocytidine monohydrochloride (B-isomer)

DOSAGE FORM
Vials

ROUTE OF ADMINISTRATION
Intravenous (I.V.)

STRENGTH(S)
200 mg vial
1 g vial

PROPOSED INDICATIONS FOR USE
Pancreatic Cancer

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

IND 29,653 - Eli Lilly and Co.
DMF 5919 - Eli Lilly and Co.
DMF 4377 - Mobil Chemical Co.
DMF 1572 - Chevron Chemical Co.
DMF 1504 - Eastman Kodak Co.
DMF 4700 - Eli Lilly and Co..
DMF 10095 - Wheaton Glass Products
DMF 6059 - Comar Glass Division, Comar Inc.
DMF 1546 - The West Co./Pharmagummi
DMF - Submitted Dec. 19, 1994 for parenteral packaging - Eli Lilly and Co.

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

■ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

■ PRESUBMISSION ☐ ORIGINAL APPLICATION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

■ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Summary (21 CFR 314.50 (c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
X	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
M. W. Talbott, Ph.D. Director		12/22/94

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*
Lilly Corporate Center Indianapolis, IN 46285	(317) 276-2574

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. *0910-0297*
Expiration Date: *November 30, 1996.*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

C/O M. W. Talbott, Ph.D.
Director
Worldwide regulatory Affairs

3. TELEPHONE NUMBER *(Include Area Code)*
(317) 276-2574

4. PRODUCT NAME
Gemzar (gemcitabine)

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☐ YES ■ NO
This is an original NDA Pre-submission, without Clinical D

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

7. LICENSE NUMBER/NDA NUMBER
20-509

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES ☐ NO *(See reverse if answered YES)*

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO *(See reverse if answered YES)*

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
M. W. Talbott, Ph.D.	Vice president ~~Director~~	12/22/94

FORM FDA 3397 (12/93)

INSTRUCTIONS FOR COMPLETING USER FEE COVER SHEET
FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplement submitted to the Agency on or after January 1, 1994. The Prescription Drug User Fee Act of 1992, Public Law 102-571, authorizes the collection of the information requested on this form to implement the Act. Failure to complete this form may result in delay in processing of the submission.

ITEM NOS. **INSTRUCTIONS**

1 - 3 Self-explanatory.

4 **PRODUCT NAME** - Include the generic name and the trade name, as applicable.

5 If clinical data are required for approval, then the application should be identified as containing clinical data. Please refer to the FDA policy regarding clinical data, Interim Guidance, Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under The Human Prescription Drug User Fee Act of 1992, July 12, 1993. Copies may be obtained from: Food and Drug Administration; Office of Small Business, Scientific and Trade Affairs; 5600 Fishers Lane, HF-50; Rockville, MD 20857. Please include two (2) pre-addressed mailing labels with your request.

6 **USER FEE I.D. NUMBER - PLEASE MAKE SURE THIS NUMBER AND THE NUMBER ON THE APPLICATION PAYMENT CHECK ARE THE SAME.** FOR APPLICATIONS SUBJECT TO USER FEE PAYMENT, please supply the following identifying information:

FOR DRUG PRODUCTS - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research Central Document Room, at (301) 443-8269.

FOR BIOLOGIC PRODUCTS - The first 4 characters are the U.S. License Number, including leading zeros; the second characters are the product code (2 letters followed by 2 numbers); and the last 7 characters are the date on the cover letter of the submission, in the format: DDMONYR. If the facility is unlicensed, or the product code is unknown, a number can be obtained by calling the Center for Biologics Evaluation and Research, at (301) 594-2906.

EXAMPLE: For U.S. License Number 4, product code ZZ01, with a document submission date of 8/3/93, the number would be: 0004ZZ0103AUG93.

7 **LICENSE NUMBER/NDA NUMBER**

FOR BIOLOGIC PRODUCTS - Indicate the U.S. License Number. If the facility is unlicensed, leave this section blank.

FOR DRUG PRODUCTS - Indicate the NDA number, if known, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 443-0035.

EXAMPLE: For NDA99999, the number would be: N099999.

8 **EXCLUSIONS** - Check the appropriate box if this application is NOT covered by user fees because it is excluded from the definition of "human drug application" as defined in Section 735(1) and (2) of the Prescription Drug User Fee Act.

Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); or NOT a new indication for use.

9 **WAIVER** - Complete this section only if the application has qualified for the small business exception or a waiver has been granted for user fees for this application. A copy of the official FDA notification that the waiver has been granted must be provided with this submission.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-509

JAN 27 1995

Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Attention: M. W. Talbott, Ph.D.
Director, Worldwide Regulatory Affairs

Dear Dr. Talbott:

We have received your presubmission of chemistry, manufacturing and controls, and pharmacology information for the following:

Name of Product: GEMZAR, gemcitabine hydrochloride, for Injection

Date of Application: December 22, 1994

Date of Receipt: December 23, 1994

Our Reference Number: NDA 20-509

We will review this early submission as resources permit. We will not, however, consider it subject to a review clock or to a filing decision by FDA. If you have any questions regarding this information, please contact:

Linda McCollum
Consumer Safety Officer
(301) 594-5756

Our willingness to accept your pre-submission is based upon the condition that the full application will be submitted no sooner than 90 days nor later than 120 days from the date of your submission.

Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Sincerely yours,

Dorothy Pease
Acting Chief, Project Management Staff
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

MWT FEB 9'95

EXHIBIT IX

Letter Submitting NDA
(Part 2 of 2)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

February 1, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20852

Re: NDA 29-509--Gemzar® (gemcitabine hydrochloride)

This letter accompanies submission of an original New Drug Application (NDA) for Gemzar® (gemcitabine hydrochloride). Gemzar is a new intravenous oncolytic agent being submitted for the indication of pancreatic cancer. This application is formatted and organized according to 21 CFR § 314.50 and follows the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications."

A pre-submission was made to this NDA on December 22, 1994 containing the chemistry, manufacturing and control data and the nonclinical pharmacology and toxicology data. This submission completes the initial NDA and provides the clinical, statistical, and pharmacokinetic data. A minor amendment to Item 3, the chemistry, manufacturing and control data, is also included. The initial User Fee due for this submission has already been paid; Form 3397 is provided.

The following summarizes the interactions and agreements reached with the Division of Oncology and Pulmonary Drug Products during the clinical investigations of gemcitabine under IND 29,653 as regards submission of an NDA for pancreatic cancer.

January 28, 1987	The initial IND (29,653) for gemcitabine was submitted.
January 24, 1992- March 31, 1992	End-of-Phase 2 meeting and conference calls: During these meetings, the protocol designs for the two studies to be used to fulfill the requirements to support registration in pancreatic cancer were developed with the advice and concurrence of the Division. Both trials were designed with clinical benefit response, a composite variable consisting of pain (pain intensity and analgesic consumption), performance status, and weight gain, as the primary endpoint. The first trial is a multi-center, single-blind, randomized, controlled study of gemcitabine versus with 5-Fluorouracil (5-FU) in previously untreated patients, Protocol B9E-MC-JHAY (JHAY). The second trial, Protocol B9E-MC-JHAZ (JHAZ), is a multi-center, single-arm study in 5-FU refractory patients. The final protocols were submitted to FDA on April 22, 1992.

Gemzar® (gemcitabine hydrochloride)
NDA 20-509

December 17, 1993 — NDA formatting meeting:

During this meeting, several agreements were reached between Lilly and the FDA regarding the content of the NDA. It was agreed that full reports would be submitted for all pancreatic cancer studies while reports for all studies conducted in all other indications would be summaries or synopses. It was agreed that all clinical report forms (CRFs) would be provided for the pivotal studies, JHAY and JHAZ, and the notable patients (deaths, discontinuations due to adverse events, and serious, unexpected, possibly causally-related adverse events) from the other pancreatic cancer studies. For studies in all other indications, the Division agreed to accept patient summaries rather than CRFs, but retained the right to request additional CRFs during the review. Agreement was reached that the integrated safety analysis should be divided into three groups: A) studies at the recommended dose and schedule (all indications) B) the pancreatic cancer studies (a subset of A), and C) all other studies. The Division agreed that the Lilly database for reporting serious adverse events (DEN) would be appropriate to use for the data in the NDA from the data cut-off date to the date of submission and for the required safety updates. Information was also exchanged about the requirements for electronic submission of the statistical and pharmacokinetic analyses.

October 31, 1994 — pre-NDA Meeting

Lilly presented the results of the pivotal trials, JHAY and JHAZ. The Division provided lists of recommended additional data presentations for both efficacy and safety. Lilly was asked to use the Cox proportional hazards models to explore prognostic factors. Requests for additional pharmacokinetic analyses were also received. Lilly was asked to provide all clinical report forms for the supporting pancreatic cancer studies, B9E-MC-JHAL, B9E-MC-JHAL (ext) and B9E-EW-E012, in addition to JHAY and JHAZ. Lilly suggested that all CRFs to be submitted be provided as CD-ROM electronic images. Following the meeting, it was agreed by teleconference this would appropriate and that paper CRF copies would not be provided.

To coordinate our activities with yours, we suggest that any written communications, regardless of subject, concerning this application be directed to:

Dr. Timothy R. Franson
Executive Director
North American Regulatory Affairs
317-277-1324
317-873-0592 (home)

Telephone calls or faxes, regardless of subject, should be made to:

Dr. Kelly Freeman
Regulatory Scientist
North American Regulatory Affairs
317-276-1337
317-823-4082 (home)
FAX number: 317-276-1652

or in her absence to:

Dr. Timothy R. Franson
Executive Director
North American Regulatory Affairs
317-277-1324
317-873-0592 (home)

Any telephone calls related to manufacturing and control issues should be made to:

Dr. Gregory Davis
Director
Regulatory Affairs, Chemistry, Manufacturing and Control
317-276-4125

or in his absence to:

Dr. Richard Raths
Head
Regulatory Affairs, Chemistry, Manufacturing and Control
317-276-4248

Any calls relating to toxicology or pharmacology issues should be made to:

Dr. Douglas Morton
Vice President
Toxicology
317-277-4301

or in his absence to:

Dr. Homer Pearce
Vice President
Cancer Research
317-276-6349

On holidays, Saturdays, or Sundays, call Dr. Freeman or Dr. Franson at home using the telephone numbers indicated. Close liaison between the Lilly personnel will result in any messages, no matter how received, being brought to the attention of all concerned.

Gemzar® (gemcitabine hydrochloride)
NDA 20-509

Please call Dr. Kelly Freeman at 317-276-1337 or me at 317-277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson MD

Timothy R. Franson, M. D.
Executive Director
North American Regulatory Affairs

TRF:ajf
Enclosures
cc: Ms. Linda McCollum (cover letter only)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: June 30, 1991
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT
ELI LILLY AND COMPANY

DATE OF SUBMISSION
February 1, 1995

ADDRESS *(Number, Street, City, State and Zip Code)*
Lilly Corporate Center
Indianapolis, IN 46285

TELEPHONE NO. *(Include Area Code)*
(317) 276-2000

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
NDA 20-509

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
gemcitabine hydrochloride

PROPRIETARY NAME *(If any)*
Gemzar

CODE NAME *(If any)*
LY264368

CHEMICAL NAME
2'-deoxy-2', 2-difluorocytidine monohydrochloride (B-isomer)

DOSAGE FORM
Vials

ROUTE OF ADMINISTRATION
Intravenous (I.V.)

STRENGTH(S)
200 mg vial
1 g vial

PROPOSED INDICATIONS FOR USE

Pancreatic Cancer

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

IND 29,653 - Eli Lilly and Co.
DMF 5919 - Eli Lilly and Co.
DMF 4377 - Mobil Chemical Co.
DMF 1572 - Chevron Chemical Co.
DMF 1504 - Eastman Kodak Co.
DMF 4700 - Eli Lilly and Co.
DMF 10095 - Wheaton Glass Products
DMF 6050 - Comar Glass Division, Comar Inc.
DMF 1546 - The West Co./Pharmagummi
DMF H1255 - Eli Lilly and Co.
Submitted Dec. 19, 1994 for parenteral packaging

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

■ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION
■ ORIGINAL APPLICATION
☐ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

■ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Summary (21 CFR 314.50 (c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
X	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
X	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
X	10. Statistical section (21 CFR 314.50 (d) (6))
X	11. Case report tabulations (21 CFR 314.50 (f) (1))
X	12. Case reports forms (21 CFR 314.50 (f) (1)) Including CD-ROM electronic CRFs
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Timothy R. Franson, M.D. Executive Director	Timothy R. Franson, M.D.	2/1/95
ADDRESS *(Street, City, State, Zip Code)* Lilly Corporate Center Indianapolis, IN 46285		TELEPHONE NO. *(Include Area Code)* (317) 277-1324

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec.1001.)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. *0910-0297*
Expiration Date: *November 30, 1996.*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

C/O Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

3. TELEPHONE NUMBER *(Include Area Code)*
(317) 277-1324

4. PRODUCT NAME
Gemzar (gemcitabine hydrochloride)

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ■ YES ☐ NO
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER
2726

7. LICENSE NUMBER/NDA NUMBER
NDA 20-509

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES *(See reverse if answered YES)* ■ NO

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES *(See reverse if answered YES)* ■ NO

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Timothy R. Franson MD	Executive Director	2/1/95

FORM FDA 3397 (12/93)

INSTRUCTIONS FOR COMPLETING USER FEE COVER SHEET
FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplement submitted to the Agency on or after January 1, 1994. The Prescription Drug User Fee Act of 1992, Public Law 102-571, authorizes the collection of the information requested on this form to implement the Act. Failure to complete this form may result in delay in processing of the submission.

ITEM NOS.	INSTRUCTIONS
1 - 3	Self-explanatory.
4	**PRODUCT NAME** - Include the generic name and the trade name, as applicable.
5	If clinical data are required for approval, then the application should be identified as containing clinical data. Please refer to the FDA policy regarding clinical data, Interim Guidance, Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under The Human Prescription Drug User Fee Act of 1992, July 12, 1993. Copies may be obtained from: Food and Drug Administration; Office of Small Business, Scientific and Trade Affairs; 5600 Fishers Lane, HF-50; Rockville, MD 20857. Please include two (2) pre-addressed mailing labels with your request.
6	**USER FEE I.D. NUMBER - PLEASE MAKE SURE THIS NUMBER AND THE NUMBER ON THE APPLICATION PAYMENT CHECK ARE THE SAME.** FOR APPLICATIONS SUBJECT TO USER FEE PAYMENT, please supply the following identifying information: **FOR DRUG PRODUCTS** - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research Central Document Room, at (301) 443-8269. **FOR BIOLOGIC PRODUCTS** - The first 4 characters are the U.S. License Number, including leading zeros; the second characters are the product code (2 letters followed by 2 numbers); and the last 7 characters are the date on the cover letter of the submission, in the format: DDMONYR. If the facility is unlicensed, or the product code is unknown, a number can be obtained by calling the Center for Biologics Evaluation and Research, at (301) 594-2906. **EXAMPLE:** For U.S. License Number 4, product code ZZ01, with a document submission date of 8/3/93, the number would be: 0004ZZ0103AUG93.
7	**LICENSE NUMBER/NDA NUMBER** **FOR BIOLOGIC PRODUCTS** - Indicate the U.S. License Number. If the facility is unlicensed, leave this section blank. **FOR DRUG PRODUCTS** - Indicate the NDA number, if known, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 443-0035. **EXAMPLE:** For NDA99999, the number would be: N099999.
8	**EXCLUSIONS** - Check the appropriate box if this application is **NOT** covered by user fees because it is excluded from the definition of "human drug application" as defined in Section 735(1) and (2) of the Prescription Drug User Fee Act. Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic Act, are excluded from application fees if: they are **NOT** for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); or **NOT** a new indication for use.
9	**WAIVER** - Complete this section only if the application has qualified for the small business exception or a waiver has been granted for user fees for this application. A copy of the official FDA notification that the waiver has been granted must be provided with this submission.

EXHIBIT VIII

Receipt Letter from FDA
For NDA Submission
(Part 1 of 2)

EXHIBIT VI

Letter From FDA
Confirming Lifting of Clinical Hold

EXHIBIT VII

Letter Submitting NDA
(Part 1 of 2)
NDA (Part 1 of 2) is Pre-submission of Chemistry, Manufacturing and Control Data and Non-clinical Pharmacology and Toxicology Data

Note to Reviewers:

For your convenience, the following conventions have been used for cross-referencing:

Item 4: Nonclinical Pharmacology and Toxicology - Within the summary reports, cross-references to the technical reports are indicated by the report number and/or the volume and page location.

Item 8 and

Item 10: Clinical and Statistical Sections - As applicable, tabbed sections have been placed at the back of each volume to provide cross-references by alphabetical / numerical order for each of the following:

Study Report Cross References: Location of the study report, case report form tabulations, and CRF image locations on CD-ROM

Patient efficacy summaries (Patients with clinical benefit response or tumor response): Location of the patient summaries and CRF images on CD-ROM

Patients who died on study: Location of the patient summaries and CRF images on CD-ROM

Patients who discontinued for an adverse event: Location of the patient summaries and CRF images on CD-ROM

Patients who experienced a serious, unexpected, possibly causally related adverse event: Location of the patient summaries and CRF images on CD-ROM

Item 12: Volume 2.132 contains the complete set of the Item 8 cross-references and because of its small size, it may be useful for you to use as a reference volume.

Lilly clinical protocols use the following naming convention, X0X-XX-XXXX. The first three digits are a project specific code, the next two are a country code, and the last four are assigned in a sequential fashion for each protocol within a country. The project code for gemcitabine is B9E; all study names begin with that code. Protocols monitored in the United States use MC for the second code and the last 4 digits were assigned sequentially as JHAA, JHAB, JHAC, etc. Studies monitored by the Lilly affiliate in the United Kingdom use EW for the country code and the last four digits were assigned sequentially as E001, E002, E003, etc. Since only the last four letters are unique to each gemcitabine protocol, please note these studies are often referred to by only the last four letters/digits, eg. JHAA or E001. Protocols monitored by Lilly affiliates in countries other than the US and the UK, are often referred to by both their country and protocol code, eg. AY-0010.

Patients are referred to using the following convention: protocol code-investigator number-patient number. So Patient B9E-MC-JHAA-001-0002 or JHAA-001-0002 refers to patient 2 treated by investigator 1 in protocol JHAA.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-509

TRF MAR 1 4 1995

FEB 1 6 1995

Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

Dear Dr. Franson:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Product:	GEMZAR, gemcitabine hydrochloride, for Injection
Therapeutic Classification:	P
Date of Application:	February 1, 1995
Date of Receipt:	February 2, 1995
Our Reference Number:	NDA 20-509

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 3, 1995 in accordance with 21 CFR 314.101(b).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone

report, or if you have any questions concerning this NDA, please contact:

Linda McCollum
Consumer Safety Officer
(301) 594-5771.

Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Sincerely yours,

Dorothy Pease

Dorothy Pease
Acting Chief, Project Management Staff
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-509

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

MAY 15 1996

Attn: Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

Dear Dr. Franson:

Please refer to your February 2, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gemzar, (gemcitabine hydrochloride) for Injection.

We acknowledge receipt of your amendments dated April 17, May 9, June 1 and 19, July 26, September 28, and October 2, 1995, as well as January 9, March 1 and 13, April 3, 17 and 24, and May 1 and 10, 1996.

This new drug application provides for the first-line treatment of patients with advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients previously treated with 5-FU.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved as effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug. Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-509. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

TRF MAY 20 1996

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21CFR 314.80 and 314.81.

If you have any questions, please contact Linda McCollum, Consumer Safety Officer, at (301) 594-5771.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

Gemcitabine, Regulatory Activity
1/28/87 through 5/15/96

DATE	ACTIVITIES
01/28/87	IND submission
02/03/87	FDA Letter - Acknowledge receipt of IND and assign IND #29,653
02/27/87	FDA telephone call - IND placed on clinical hold
04/13/87	Letter to FDA - response to clinical hold issues
04/29/87	Telephone call to FDA: status of clinical hold
05/04/87	Telephone call to FDA: status of clinical hold
05/06/87	Telephone call to FDA: status of clinical hold; CMC issues
05/12/87	Telephone call from FDA: clinical hold released
05/18/87	Submission to FDA-IND amendment
05/18/87	Submission of Toxicology report #9
06/04/87	Amendment to protocol JHAC
06/18/87	FDA Letter - Acknowledgment of amendments dated Apr. 13 and May 18, 1987. Clinical hold release confirmed with some requests and recommendations (also referenced May 12 telephone conversation)
06/30/87	Chemistry submission
08/06/87	Protocol JHAB
08/14/87	Clinical Investigators Brochure submitted
08/18/87	Telephone call from FDA; clinical protocol question
08/18/87	Protocol JHAA
10/08/87	Response to clinical question on JHAB
10/19/87	Request to export for clinical trial
11/27/87	FDA Letter - Acknowledge receipt of letter dated Oct. 19, 1987 requesting authorization to export to France
12/03/87	Request to export for clinical trial
12/18/87	Submission of Toxicology reports #10 & #11
01/14/88	FDA Letter - Acknowledge receipt of letter dated Dec. 3, 1987 requesting authorization to export to Amsterdam, The Netherlands
01/26/88	Reply to letter dated Oct. 19, 1987 - authorization to ship drug to France
02/01/88	Annual Report
02/10/88	Telephone call from FDA-annual report question
03/09/88	FDA Letter - Reply to letters dated Dec. 3, 1987 and Jan. 4, 1988 - authorization to ship drug to Amsterdam
07/15/88	Interim laboratory information forwarded to Investigators
07/28/88	Investigator Documents
09/14/88	Amendment to JHAA; updated Clinical Investigators Brochure
09/20/88	Amendment to JHAB
09/28/88	Chemistry submission
12/14/88	Amendment to JHAC
01/05/89	Chemistry submission (14C Labeled)
01/11/89	Amendment to JHAC
01/19/89	Amendment to JHAC
01/24/89	Tables for protocol JHAC
01/26/89	Annual Report
02/06/89	Amended Protocol JHAA
02/08/89	Telephone call to FDA - clinical question
03/07/89	Meeting with FDA and Lilly - discussion of clinical trial designs

03/27/89	Summary of 3/7 meeting
04/14/89	Letter from FDA-guidelines for ovarian and colon cancer; 3/7/89 meeting minutes
04/26/89	Label; Toxicology Report #12 (Immunogenicity)
05/18/89	Toxicology report #13 (Hazard Evaluation)
06/14/89	Amendment to Protocol JHAC
08/10/89	Chemistry submission (Revised method of synthesis)
08/30/89	Protocol JHAD
08/31/89	Amendment to JHAA
09/18/89	New protocols JHAE & JHAF; Amendment to JHAD
09/19/89	Emergency use request
10/23/89	Revised protocols JHAE & JHAF; New protocols JHAH & JHAL; labels
10/27/89	Emergency use request
10/31/89	Follow-up telephone call on emergency use request of 10/27/89
11/15/89	Addendum to JHAD, Investigator documents, Toxicology; revised brochure
11/22/89	Protocol JHAK
12/05/89	Amended protocols JHAE(c), JHAF, JHAH, JHAK, JHAL
01/08/90	Protocols JHAG, JHAI, new Investigator documents
01/29/90	Investigator Document
01/29/90	Annual Report
02/08/90	Amended protocol JHAG
02/15/90	Amended protocol JHAD
02/19/90	Protocols (JHAN & JHAO - Canadian protocols) Submitted for information only. FDA will not accept; resubmitted 5/17/90.
03/01/90	Investigator Documents
03/06/90	Protocol JHAH
03/16/90	New amendment; Protocols JHAJ - new & JHAI - amended
03/19/90	Telephone call to FDA - clinical item
03/19/90	Investigator Documents
03/20/90	Correspondence
03/28/90	Letter
03/30/90	Investigator Documents
05/02/90	Investigator Documents
05/17/90	Protocol (JHAN & JHAO - Canadian Protocols) (Resubmitted per FDA); New Investigator Documents
06/12/90	New Investigator Documents
07/19/90	Amendment to Protocol JHAA (b)
08/08/90	Correction submission on new Investigator Documents; Sub-Investigators
08/30/90	New Investigator Documents
09/01/90	Letter to FDA
09/18/90	Amendment to protocol JHAL(b); New Investigator Documents
09/21/90	Final Report JHAA
10/05/90	Corrected pages to Final Report JHAA
10/08/90	Amended protocol (JHAG)
10/23/90	Telephone call to FDA: clinical items
10/25/90	Toxicology Report #14
11/09/90	Final Report JHAC
11/12/90	Sub-Investigator and new Investigator Documents
11/19/90	New Protocol JHAP, New Investigator Documents (JHAG-201)
12/18/90	Letter to FDA and attachments
12/21/90	Letter to FDA
01/07/91	Sub-Investigator, CT Labels
01/07/91	Amended Protocol JHAN, Toxicology Report #16
01/10/91	Amended protocols JHAJ & JHAI
01/15/91	Amended Protocol JHAE(d)

01/16/91	Amended Protocol JHAH
01/24/91	Amended protocol JHAA(c) & JHAD(d)
01/25/91	New Investigator for JHAI & JHAH, new sub-investigators
01/25/91	Letter to FDA
01/28/91	Final report JHAB
01/29/91	Annual Report
02/04/91	Amended protocol JHAD
02/08/91	Amended Protocol JHAG(c)
02/20/91	Amended Protocol JHAO (CA protocol)
02/21/91	Letter to FDA (request for meeting)
02/25/91	Letter to FDA
03/14/91	New Protocols JHAQ & JHAR and new investigator
03/25/91	New Protocol JHAS & New Investigator, CT labels and chemistry Information
04/01/91	New protocol JHAT & new investigator & new Sub-Investigator
04/10/91	Letter to FDA
04/11/91	Amended protocols JHAA, JHAD, JHAG, JHAL, JHAP - new sub-investigators, CT Labels
04/12/91	Amended protocols JHAI, JHAJ, JHAQ, JHAR
04/12/91	Amended protocols JHAH, JHAK, JHAF
04/18/91	Telephone call to FDA; discussion of protocol JHAS
04/23/91	Letter to FDA
04/25/91	New protocol JHAW, New Investigator
05/14/91	Protocol and investigator JHAV
05/20/91	Telephone call from FDA: discussion of protocol JHAW
06/11/91	New protocol JHAX, Investigator documents
06/12/91	Emergency use request
06/13/91	Telephone call from FDA on emergency use request
06/24/91	Amended protocol JHAL
06/25/91	Toxicology Report #17 ,Sub-Investigator
06/27/91	Letter to FDA
06/28/91	Letter to FDA
07/01/91	New protocol JHAL, New investigator
07/11/91	Cover letter and draft of JHAY protocol
07/12/91	Amendment to protocol JHAE(e)(1) and addendum CT Labels
07/22/91	Meeting with FDA and Lilly to discuss clinical trial endpoints
08/01/91	Letter to FDA w/ attachments (Minutes of 7/22/91 meeting)
08/08/91	Sub-Investigator document and Toxicology Report #24
08/22/91	(Correspondence) Letter to FDA and attachments
08/27/91	Letter to FDA
08/30/91	Protocol amendment JHAX
09/09/91	Amendment to protocol JHAE(f) new Sub-Investigator
09/10/91	Amendment to protocol JHAR(b)
09/16/91	Toxicology report #18
09/18/91	Toxicology report #22
09/25/91	Toxicology Report #8 (corrected pp. 10) Original submission 1-28-87 Protocol JHAL(c)
09/27/91	Letter to FDA and Protocol (for FDA information only)
09/30/91	Toxicology Report
10/03/91	Amended Protocol (JHAD)
10/10/91	Toxicology Report #21
10/25/91	Letter of FDA and attachments (Summary of Strategy of Protocols for Pancreatic Cancer)
10/28/91	Toxicology Reports #23 and #26, CT labels
10/29/91	Amendment to Protocol JHAX, SUB-Investigator Document
10/29/91	Correction letter to FDA re: 10/10/91 submission

11/07/91	Amendment Protocol JHAL (d)
11/22/91	Amendment Protocol JHAL (c)
12/09/91	Letter to FDA re: Protocol JHAD
12/18/91	Letter to FDA re: Jan. 92 meeting and Draft Protocols
01/21/92	Pharmacology Reports #1 & #2
01/27/92	ADME Report
01/27/92	Annual Report
02/10/92	Toxicology Report #31, Sub-Investigator Documents
02/19/92	Letter to FDA, Draft of Protocols
02/21/92	Toxicology Report #20 & #28
03/04/92	Telephone call to FDA - clinical items
03/04/92	Telephone call to FDA; discuss phase 3 clinical trial designs
03/06/92	Amended Protocol JHAO, JHAX, new Investigator Documents, Sub-Investigator Documents
03/09/92	Letter to FDA
03/19/92	Telephone call to FDA - clinical items
03/20 92	Fax from FDA - comments on JHAY, JHAZ proposed protocols
03/30/92	Letter to FDA (Toxicity Summaries attached)
04/03/92	Letter to FDA and Attachments
04/14/92	Fax to FDA - statistical items
04/15/92	Amendment (b) to Protocol JHAQ, SUB-Investigator, CT labels
04/21/92	Emergency use request
04/22/92	Letter to FDA, Protocols (JHAY & JHAZ)
05/12/92	Letter to FDA-Correction of Page Numbers
05/13/92	Letter to FDA re: Correction to Protocol JHAY
05/14/92	Toxicology Report #27 & #29, Clinical Trial Labels
05/19/92	Letter to FDA
06/16/92	Telephone call to FDA - clinical items
06/16/92	Chemistry Amendment
06/22/92	FDA Letter - Recommendations on amendments for clinical protocol JHAY
06/26/92	Fax from FDA - comments on JHAY protocol
07/08/92	Protocol amendments JHAY & JHAZ
07/14/92	New Investigator, Sub-investigator & Toxicology Reports #32
07/20/92	Consent forms for Protocol amendment JHAY & JHAZ
07/29/92	Amend protocols (JHAQ(c), JHAV(a), JHAW(a)), New Investigator documents
07/30/92	Toxicology summaries - patients on JHAS & JHAU; letter to FDA
07/31/92	Amendment to protocol JHAS(a)
08/10/92	General pharmacology report No. 4
08/17/92	Emergency use request
09/01/92	New Investigator Information - letter to FDA
09/16/92	General pharmacology report No. 3 and Toxicology Report #33
09/25/92	Letter to FDA re: New Investigator for JHAY & JHAZ
09/29/92	Telephone call from FDA - clinical items
10/20/92	Amendment to protocols JHAE(g), JHAQ(d), JHAS(b), JHAT(a), JHAU(a), JHAW(b)
11/09/92	New investigator JHAY & JHAY
11/10/92	Telephone call to FDA - Canada discussion
11/12/92	Clinical Investigators Brochure, CT Label , JHAY, New Sub-Investigator JHAZ
11/19/92	Telephone call to FDA - Canada discussion
12/10/92	Telephone call from FDA - clinical items
01/13/93	New Sub-Investigators JHAZ, JHAY
01/15/93	Correspondence - letter JHAY
01/29/93	Annual Report (includes revised Clinical Investigator Brochure)
03/01/93	Correction letter for submission #243 - 11/9/92
03/12/93	Submission JHAZ/JHAY Toxicology report #35

03/23/93	Sub-Investigators/Additional Lab sites
04/21/93	Toxicology Report #19 - Sub-Investigators JHAV, JHAY, JHAZ
05/06/93	Revised pages general pharmacology #2 - pg. 10, Toxicology Report #12 - pg 7
06/03/93	New Investigator documents, SUB-Investigator documents, Toxicology Report #36
06/25/93	New protocol JHBB
07/07/93	Toxicology report #30
07/13/93	Emergency use request
08/04/93	New protocols JHCD, JHCE, JHCF new investigators, new sub-investigators, new study sites
09/01/93	Telephone call and Fax to FDA - pre NDA meeting arrangements
09/20/93	Emergency use request
09/27/93	New protocols JHBC, JHBA amend (a) to protocol JHBB new investigators and sub-investigators
10/01/93	Pre-NDA meeting information package
10/11/93	Revised Clinical Investigators Brochure
10/12/93	Emergency use request
11/23/93	Telephone call to FDA - clinical items
12/02/93	New protocol JHBJ, New investigator
12/20/93	New protocol JHBD, New Investigator documents, sub-investigator and clinic dates
12/23/93	Letter to FDA - Request Pre-NDA meeting
01/04/94	Correction letter for Submission on Dec. 20, 1993
01/13/94	Amendment to JHBA, JHBC(a) JHBI(b), JHAZ(b), New investigator JHAC, P016
01/27/94	Annual Report (Revised Clinical Investigators Brochure)
01/28/94	New Protocol JHBH, New Investigator
02/01/94	Letter to FDA request for meeting
02/02/94	New Protocol JHCG
02/07/94	Withdrawal Letter Protocol JHCG
02/07/94	FDA Letter
02/10/94	Telephone calls to FDA - clinical items
02/10/94	New Investigator documents, Add clinical site, New Sub-Investigator documents
02/14/94	Emergency use request
02/14/94	New Protocol JHCG (re-submitted)
02/28/94	New Protocol JHBK, CT Labels
03/09/94	New SUB-Investigator-study and lab site change, New Investigator Documents JHBC
03/16/94	Amendment Protocol JHAY(c)
03/28/94	Correspondence to FDA (attendees for 4/94 meeting)
03/31/94	Amendment to JHBC
04/13/94	New Investigator JHCG, Sub-investigators
05/04/94	FDA Meeting Packet
05/19/94	New Investigator Documents and SUB-Investigator Documents
05/25/94	New Investigator Documents
07/18/94	Telephone call to FDA - pre-NDA meeting arrangements
07/29/94	Investigator Documents, site change
08/05/94	Telephone call to FDA - clinical items
08/09/94	Pre Meeting Binder/Minutes from 4/19/94 meeting
08/15/94	Pre NDA Meeting Binder update
08/17/94	Protocol Amendments JHBB(b), JHBA(d)
08/22/94	Supplied for our information - meeting minutes from Pre-NDA mtg. of Dec. 17, 1993
08/30/94	Telephone call to FDA - pre-NDA meeting arrangements
09/14/94	Sub-Investigator JHBB
09/16/94	Chemistry amendment
09/20/94	Protocol JHDN submitted as correspondence for FDA comments only, not as a protocol Submission. Four desk copies sent to Linda McCullum, FDA
09/29/94	Update of Material for pre-NDA Meeting

10/04.94	Emergency use request
10/22/94	NDA Presubmission of CMC section
11/02/94	JHBK - A Phase 2 Trial with Gemcitabine in Patients with Cancer of the Urothelium
11/03/94	FAX from Linda McCullum, FDA - re Pre-NDA data
11/08/94	Slides from PreNDA Meeting
11/11/94	FAXed emergency use request to FDA
12/08/94	FAXed emergency use request to FDA
12/14/94	Cover letter for protocol JHEK
12/21/94	FAXed emergency use request to FDA
12/29/94	IND 29,653 - Gemcitabine - TREATMENT PROTOCOL JHEW
01/05/95	FAXed emergency use request to FDA
01/10/95	IND 29,653 - Gemcitabine (JHEW), Annual Report Extension Request
01/12/95	Amendment (a) and (b) were submitted together on Serial #375 - IND 29,653 - Gemcitabine - TREATMENT PROTOCOL JHEW
01/12/95	FAXed emergency use request to FDA
01/13/95	Letter from Charles P. Hoiberg - FDA received JHEW Dec. 30, 1995 - IND 29,653 - Gemcitabine - TREATMENT PROTOCOL JHEW
01/27/95	Letter from Janet Woodcock - FDA received JHEW Dec. 30, 1995 IND 29,653 - Gemcitabine - TREATMENT PROTOCOL JHEW
01/27/95	NDA Part 1 of 2, Date of Application: 22-Dec-1994, Date of Receipt: 23-Dec-1994
01/29/95	Dr. R. Raths, Ms. T. Lawhon phone con. to Dr. Paul Dietze, FDA
01/29/95	Dr. R. Raths, Ms. T. Lawhon phone con. to Dr. Paul Dietze, FDA
02/01/95	FAXed emergency use request to FDA
02/01/95	Initial Application of NDA
02/07/95	Amendment (c) IND 29,653 - Gemcitabine - TREATMENT PROTOCOL JHEW
02/09/95	FAXed emergency use request to FDA
02/09/95	Response to request for additional desk copies of NDA Volume 2.1 from Linda McCollum - FDA
02/16/95	Acknowledgement of Receipt of NDA 20-509
02/23/95	Request for Emergency use
04/17/95	Attachments included. Additional (2) desk copies to Linda McCullum, CSO
04/21/95	Three copies of Serial No. 355 to Linda MCCullum, FDA
04/26/95	FAXed emergency use request to FDA
04/28/95	Re: Safety Update
05/25/95	FAX to Linda MCCullum, FDA re 1572 forms and working with oncology cooperative groups
06/01/95	4-month safety up-date
06/09/95	FAX from Sue-Jane Wang, G. Schechter and Steve Wilson of DOPDP, FDA. Additional needed information for Gemcitabine NDA 20-509
06/12/95	Response to request from Linda MCCullum, CSO for CM&C volumes 1.1 through 1/14A of NDA 20-509
06/12/95	FAX from Sue-Jane Wang, G. Schechter and Steve Wilson of DOPDP, FDA. Additional needed information for Gemcitabine NDA 20-509
06/13/95	Response to 6/9/95 and 6/12/95 Statistics requests from FDA
06/13/95	Re: FDAs stats requests
06/19/95	Statistical Request for electronic files
06/26/95	ODAC Briefing Materials for July 24, 1995 Meeting of the Oncologic Drugs Advisory Committee
06/29/95	Request from Dr. G. Schechter for new copy of CD-ROM disk previously submitted and for hard copy of patients CRFs. These were included with the cover letter noted in the electronic file
06/29/95	FAX to Linda MCCullum, FDA re: corrections found in the NDA study reports for JHAY & JHAZ
07/05/95	This submission also contains paper section, new investigator information for treatment

	protocol JHEW
07/06/95	Request from Dr. G. Schechter for copies of patients CRFs. First batch sent June 29, 1995. JHAL CRFs included in this 7/6/95 submission
07/19/95	FAX containing Dr. G. Schechter's review of Gemzar pancreas submission - it was sent in 7 sections
07/21/95	Cover letter for Protocol JHEE and investigator data
07/26/95	Cover letter for JHES 001 & 002 investigator data
07/26/95	CM&C Amendment
07/27/95	Request for Electronic data - Diskette sent with this cover letter
08/22/95	Phone conversation with Linda McCullum, CSO at FDA re Gemzar application
08/24/95	Phone conversation with Linda McCullum, CSO at FDA re data analyses
08/25/95	FAX to Linda McCullum, CSO at FDA re data analyses
08/28/95	FAX received from Linda McCullum/Dr. Schechter dated 8/28/95 responding to 8/25/95 communication
08/30/95	NTF re telephone request received from Ms. Linda McCullum on 8/25/95 requesting ok to release gemcitabine information to congressman Kingston and/or Mr. Tony Parrish
08/31/95	NTF re FAX received from Dr. Schechter dated 8/28/95 responding to our 8/25/95 communication
09/05/95	Correction to 9/1/95 (Serial. no. 420) submission
09/07/95	Re FDA's furlough starting 10/1/95 because of the government budget procedure. Our request for information regarding our Gemzar "letter", and our data issues summary being prepared for their review
09/15/95	Cover letter for amendments for reports JHAY, JHAZ and integrated summary of safety information previously submitted in the NDA
09/22/95	FAXed document - cover letter re results for JHAY and JHAZ that are presented in the draft medical review sent to us just before the ODAC meeting
09/22/95	Re phone conversation of 9/22/95 between Kelly Freeman and Linda McCullum
09/28/95	Cover letter re results for JHAY and JHAZ that are presented in the draft medical review sent to us just before the ODAC meeting
09/28/95	Fax - List of NDA deficiencies for CMC
09/29/95	Copy of FAX for emergency use request and approval from FDA
10/20/95	Dr. Dietze's response to clarifications
10/23/95	List of investigators for TX IND
10/23/95	Treatment IND - Investigator Information
10/23/95	Letter to The Honorable Jack Kingston
10/24/95	Fax to Linda McCullum - Request for Emergency Use
10/25/95	Emergency Use Request
10/30/95	Response for Site Audit
11/02/95	Approval for emergency use by Drs. Strauss and Young
11/09/95	Response to correspondence of September 28, 1995. - Linda McCullum
11/10/95	Response to FAX from Linda McCullum - CT/Ultrasound Scans
11/19/95	Follow-up to Dr. Hom - Call from Linda McCullum
11/21/95	Request for Emergency use
11/21/95	Emergency Use Request - Approval from Linda McCullum for Dr. Gurtler
11/22/95	Emergency Use Approval: Dr. Mittelman
11/27/95	Request for Emergency Use - Drs. Dunning and Byrne
11/28/95	Request for Emergency Use - Drs. Gersh and Atkins
11/29/95	Emergency Use Request - Approval from Linda McCullum - 4 Emergency Use Patients
12/03/95	Emergency Use Approval: Dr. L. Daubert
12/03/95	Emergency Use Approval: Dr. Mendelsohn
12/03/95	Emergency Use Approval: Dr. Phillips
12/03/95	Emergency Use Approval: Dr. Buzaid
12/04/95	Telephone call with Dr. Paul Dietze - Labeling
12/05/95	Request for Emergency Use - Dr. Radice

12/07/95	Request for Emergency Use by Dr. Elder
12/07/95	FDA request additional information for JHAY and JHAZ amendment dated September 28, 1995
12/08/95	Emergency Use Tally for Annual Report
12/08/95	Request for Emergency Use - Dr. Dunning
12/12/95	Request for Emergency Use by Dr. Shetabi
12/12/95	Request for Emergency Use by Dr. Allogood
12/12/95	Emergency use request - Dr. John Ford
12/12/95	Request for Emergency use by Dr. Allogood
12/12/95	Summary for Emergency Use Requests
12/12/95	Fax follow-up to 12/11/95 telephone conference
12/12/95	Calls from Dr. Dietze and Ms. Kelly
12/15/95	Cover letter to Roswitha Kelly with requested information for review of NDA 20-509
12/15/95	Cover letter to George Chi with requested information for review of NDA 20-509
12/20/95	Request for Emergency Use by Dr. Geister
12/20/95	Comments from Medical Reviewer
12/21/95	Emergency Use Approval: Dr. B. Geister
12/21/95	PK reviewer - Comments Labeling
12/22/95	Emergency use request approval: Dr. Ritter
12/22/95	Approved for emergency use for Dr. Ritter's patient
12/22/95	Comments from PK reviewer - Chemistry responses
01/02/96	Emergency use request: Dr. L. Mendelsohn
01/02/96	Emergency use request approval
01/02/96	Emergency use request approval
01/02/96	Emergency use request approval
01/02/96	Emergency use request approval
01/04/96	Call from Dr. Paul Dietze, RE: HCl
01/05/96	Conference call with Dr. Nguyen (Lilly) and Dr. Schechter (FDA)
01/05/96	Telephone conversation with Dottie Pease, Supervisory CSO
01/08/96	Telephone call confirmation with Ms. Dottie Pease
01/09/96	Amendment to NDA Item 3
01/11/96	Emergency use request approvals: Dr. Muss
01/11/96	Emergency use request approvals: Dr. Muscato
01/11/96	Emergency use request approvals: Dr. Gersh
01/15/96	Cumulative list of investigators
01/15/96	IND 29,653 - Gemcitabine - TREATMENT PROTOCOL JHEW -Cumulative list of investigators
01/17/96	Emergency use request approvals: Dr. Muss, Dr. Gersh, Dr. Muscato
01/17/96	Emergency use request approval for Dr. O'Shaughnessy
01/17/96	Emergency use request : Dr. L. Mendelsohn
01/17/96	Emergency use request: Dr. David Young
01/17/96	Emergency use request: Dr. Robert Johnson
01/17/96	CMC responses
01/19/96	Emergency use request: Raul Doria, MD
01/22/96	Emergency use approval: Drs. Mendelson, Young and Johnson
01/22/96	Emergency use request approval: Dr. R. Doria
01/23/96	Emergency use request: Dr. Larry Cripe
01/23/96	Emergency use request: Dr. E. Mitchell
01/23/96	Emergency use request: Dr. W. Butler
01/25/96	Emergency use request: Dr. Osborn
01/25/96	Check-in call to Dr. Paul Dietze
01/26/96	Emergency use request approval : Dr. Osborn
01/29/96	Electronic Copy of CMC Documents submitted on Jan. 9, 1996. Diskettes to: Dr. Dietze and copy of letter to Linda McCullum

01/29/96	Electronic copy of text sent to Dr. Dietze
01/30/96	Emergency use request: Dr. Hearn
01/31/96	Emergency use request approval: Dr. Hearn
01/31/96	Emergency use request approval: Dr. Edward Hearn
02/01/96	Emergency use request: Drs. Tomao and Ho
02/02/96	Emergency use request approval: Drs. Frank Tomao and Reginald Ho
02/05/96	Emergency use request: Dr. William Butler
02/06/96	Emergency use request approval: Dr. William Butler
02/07/96	Emergency use request: Dr. J. Muscato
02/09/96	Emergency use request approval: Dr. Muscato
02/09/96	Call to CSO and Medical Reviewer
02/12/96	Emergency use request: Dr. Bogart
02/14/96	Emergency use request approval: Dr. Bogart
02/14/96	FAX from Linda McCullum re comments and deficiencies from the Medical and Pharm-Tox reviews of the original NDA 20-509
02/14/96	Gemzar NDA- preliminary Medical Review is complete
02/15/96	FDA Comments-Medical/Pharm/Tox reviewers
02/19/96	Emergency use request: Dr. M. Kanojia
02/19/96	Gemzar Update-Medical and Pharm/Tox responses
02/20/96	Emergency use request approval: Dr. M. Kanojia
02/21/96	Labeling comments from PK Reviewer
02/21/96	Telephone, FAX call from FDA
02/22/96	Emergency use request from Dr. Magaral Murali
02/23/96	Emergency use request approval: Dr. Murali
02/26/96	Emergency use request from Dr. Lawrence Einhorn
02/28/96	Request for emergency use - Dr. Robert Nagourney
02/28/96	Request for emergency use - Dr. Gary Gross
02/29/96	Emergency use request approval: Drs. Einhorn, Nagourney, and Gross
03/13/96	Request for Emergency use: David Howe
03/13/96	Responses sent to FDA
03/15/96	Emergency use request approval: Dr. Howe
03/21/96	Review of Medical Responses
03/27/96	Status of Reviews - Medical and CM&C
03/29/96	Medical Review
03/30/96	Emergency use approval: Dr. Antonia
04/02/96	This submission included Gemzar Launch Material
04/03/96	Amendment to NDA Item 3
04/04/96	Draft Labeling - Call from Linda McCullum
04/09/96	Emergency use request - Dr. Roush
04/11/96	Emergency use request - Dr. Wendt
04/11/96	Emergency use request - Dr. Gunel
04/11/96	Emergency use request approval: Dr. Roush
04/11/96	Revision request for package insert
04/11/96	Revision request - package insert, vial and carton labels
04/11/96	PK and Micro Update and DDMAC Information.
04/12/96	Emergency use approval: Drs. Wendt and Gunnell
04/12/96	Amendment to NDA Item 3
04/12/96	Amendment to NDA Item 3
04/15/96	FDA Comments and Lilly Response
04/15/96	FDA comments and Lilly response
04/16/96	Cover letter to Linda McCullum and diskette sent per FDA request
04/17/96	Amendment to Item 3 CM&C section - FAX sent 4/11/96
04/17/96	Draft copies of vial labels and cartons for review
04/17/96	Corrections to FAX of 4/12/96

04/17/96	FDA Update
04/19/96	Emergency use request: Dr. Margaret Tempero
04/19/96	Emergency use approval: Dr. Margaret Tempero
04/23/96	Vial and Carton Labels
04/23/96	Microbiology, Medical, Vial and Carton Labels
04/24/96	95% Confidence Levels - JHAY - modified 4/19/96
04/24/96	Requested Safety Analysis
04/24/96	Time-to-Progressive Disease Results
04/25/96	Emergency use request: Dr. Kevin Mullins
04/25/96	Emergency use request: Dr. Siegel
04/25/96	95% Confidence Levels - JHAZ - modified 4/19/96
04/25/96	Response to FAX in RE: time to event dates
04/25/96	Requested Data - Nausea and Vomiting (pancreas and other tumor types)
04/25/96	Time-to-Progressive Disease Results
04/25/96	Reanalysed Time-to-Progressive Disease Results for Study JHAY
04/25/96	Requested Data (pancreas and other tumor types)
04/25/96	Requested data (pancreas and other tumor types)
04/25/96	Requested Data -(pancreas and other tumor types)
04/25/96	Requested Data -(pancreas and other tumor types)
04/25/96	Requested Data -(pancreas and other tumor types)
04/26/96	Response to FAX - RE: time to event dates
04/26/96	Time-to-Event Data for JHAZ
04/26/96	Reanalyzed Time-to-Event Results for Study JHAZ/Patients at Risk for each time point Studies JHAY and JHAZ
04/30/96	Emergency use request: Dr. Jacqueline Jones
04/30/96	Emergency use approval: Drs. Siegel and Mullins
04/30/96	Response to Lilly - Comments on Press Kit Materials, submitted to the Division of Drug Marketing, Advertising and Communications
04/30/96	Final-time-to-event analyses for JHAY, JHAZ
05/01/96	Emergency use request: Dr. Patrick Loehrer
05/01/96	Emergency use approval: Dr. J. Jones
05/01/96	Emergency use approval: Dr. J. Jones
05/01/96	Amendment to NDA Item 3
05/01/96	Meeting minutes regarding CMC
05/01/96	Statistical Reviewer Call and Letter Status
05/02/96	Emergency use approval: Dr. Pat Loehrer
05/02/96	Approvable letter from FDA
05/03/96	FAX from FDA DDMAC
05/03/96	Request for information
05/07/96	Gemzar Update - All responses sent to FDA
05/07/96	Gemzar Update - Revised labeling received from FDA, Initial responses sent to FDA
05/10/96	Response to Approvable Letter - Additional Information
05/12/96	Call from Dr. Schechter to discuss labeling
05/15/96	FAXed copy of "Approval for Marketing" letter - received 8:10pm on 5/15/96
05/15/96	Approval Letter from FDA

EXHIBIT X

Receipt Letter from FDA
for NDA Submission
(Part 2 of 2)

EXHIBIT XI

Letter from FDA to Lilly Indicating
NDA for Gemcitabine Hydrochloride is Approved

EXHIBIT XII

Description of Significant Activities Undertaken by Lilly with Respect to Gemcitabine Hydrochloride during the Regulatory Review Period

"Express Mail" mailing label number EM 122644328 US

Date of Deposit July 12, 1996

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231..

Margaret M. Brumm
Printed Name

Margaret M. Brumm
Signature

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,808,614

Patentee : Larry W. Hertel Attn: Box Patent Ext.

Assignee: : Eli Lilly and Company

Issue Date : February 28, 1989

LETTER OF TRANSMITTAL OF APPLICATION

FOR EXTENSION OF PATENT TERM

Assistant Commissioner for Patents

Washington, D.C. 20231

Sir:

Transmitted herewith for filing is an application for extension of term of U.S. Patent No. 4,808,614 and a duplicate thereof, certified as such.

Please charge the filing fee of $1,060 to deposit account No. 05-0840 in the name of Eli Lilly and Company. An original and two copies of this paper are enclosed. The Assistant Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to account No. 05-0840.

The application transmitted herewith has been executed by David E. Boone, an agent of the owner of record of the subject patent. Therefore, the present application is complete and

entitled to a filing date of July 12, 1996 as indicated by the Certificate of Mailing by "Express Mail".

ELI LILLY AND COMPANY

By: Margaret M. Brumm

Margaret M. Brumm
Patent Attorney
Registration No. 33,655

Phone: 317-276-0755

Eli Lilly and Company
Patent Division/MMB
Lilly Corporate Center
Indianapolis, Indiana 46285

11 July 1996

"Express Mail" mailing label number EM 122644328 US

Date of Deposit July 12, 1996

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231..

Margaret M. Bruemm
Printed Name

Margaret M. Bruemm
Signature

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,808,614

Patentee : Larry W. Hertel Attn: Box Patent Ext.

Assignee: : Eli Lilly and Company

Issue Date : February 28, 1989

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FOR EXTENSION OF PATENT TERM

Assistant Commissioner for Patents

Washington, D.C. 20231

Sir:

Transmitted herewith for filing is an application for extension of term of U.S. Patent No. 4,808,614 and a duplicate thereof, certified as such.

Please charge the filing fee of $1,060 to deposit account No. 05-0840 in the name of Eli Lilly and Company. An original and two copies of this paper are enclosed. The Assistant Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to account No. 05-0840.

The application transmitted herewith has been executed by David E. Boone, an agent of the owner of record of the subject patent. Therefore, the present application is complete and

entitled to a filing date of July 12, 1996 as indicated by the Certificate of Mailing by "Express Mail".

ELI LILLY AND COMPANY

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11 July 1996

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Margaret M. Brumm
Printed Name

Margaret M. Brumm
Signature

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 4,808,614

Patentee : Larry W. Hertel Attn: Box Patent Ext.

Assignee: : Eli Lilly and Company

Issue Date : February 28, 1989

LETTER OF TRANSMITTAL OF APPLICATION

FOR EXTENSION OF PATENT TERM

Assistant Commissioner for Patents

Washington, D.C. 20231

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